ORGANICALLY FUNCTIONALIZED MULTIPOROUS ALUMINO-SILOXANE AEROGEL MICROSPHERES FOR CONTROLLED RELEASE OF ANTIPLATLETIC DRUG: ASPIRIN

THESIS

Submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai

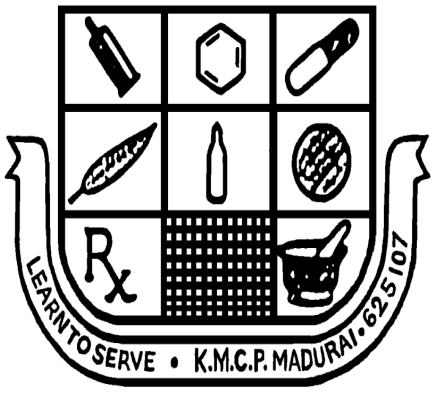
In partial fulfillment of the requirements

For the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS



DEPARTMENT OF PHARMACEUTICS

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DEDICATED TO

MY BELOVED PARENTS, TEACHERS &

FRIENDS

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"Read. Read in the name of thy Lord who created; [He] created the human being from blood clot. Read in the name of thy Lord who taught by the pen: [He] taught the human being what he did not know."

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Talasila Sindhoor

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LIST OF ABBREVATIONS

FTIR	Fourier-transform infra-red
GI	Gastrointestinal tract
HCl	Hydrochloric acid
APTMS	(3 - aminopropyl) trimethoxy silane
MCM	Mobil Composite Materials
BET	Brunauer - Emmett – Teller
BJH	Barrett - Joyner - Halenda trimethoxy silane
M41S	Mesoporous silica family
N2	Nitrogen
DDS	Drug delivery system
PBS	Phosphate buffer saline
TEOS	Tetraethyl orthosilicate
TEM	Transmission electron microscopy analysis
SEM	Scanning electron miscroscopy analysis
UV	Ultra - violet
VIS	Visible
XRD	X-ray Diffraction
SBA-15	Santa Barbara Amorphous material composition 15

1. INTRODUCTION

1.1 Drug delivery system

In the past few years there has been an exceptional growth in research focused on drug delivery systems. This tremendous growth in this field is due to the exploration in the field of medicine and possibilities that these systems offer to biomedicine, such as several drugs which have been synthesized and thereafter these drugs being formulated into suitable dosage forms for administration using new therapies which in turn improved the efficacy and safety. This gives a chance of delivering new complex drugs that otherwise would not have been possible. The improvement of therapeutic responses with continuous drug release (controlled drug release) patterns rather than pulsatile (conventional dosage forms). The opportunities that recent advances in material sciences and biotechnology offer to develop new physical and medical methods of drug delivery have to be well obliged. There has been an upward trend in designing new dosage forms and also make it biocompatible[1]. However, the real advance has emerged as the development of targeted delivery in which the drug acts in the target area of the body. For this type of system, site specific and disease specific drugs need to be used since it is vital to direct the drugs where they are specifically needed[2]. Additionally, the sustained release in which the drug is released over a period of time in a controlled fashion has also been revealed as a milestone of this type of technology.

Advances in controlled release drug delivery systems have been largely based on advances in functional polymers. However, the future of controlled release dosage forms will likely be heavily dependent upon the success of delivery approaches in the next millennium will require interdisciplinary approaches. Development of controlled release drug delivery systems requires simultaneous consideration of several factors, such as the drug property, route of administration, nature of delivery vehicle, mechanism of drug release, ability of targeting, and biocompatibility[3].

1.2 Controlled release oral drug delivery systems

In spite of rapid progress in our understanding of the fundamental biological processes underlying many diseases, the progress of a breakthrough in developing drug molecules or designing of new pharmaceutical drug delivery dosage forms in reaching the site of abnormality and achieve comparable advances in the detection, diagnosis, and mitigation of these diseases is substantially on the back foot. The need for such targeting mainly arises from the fact that most therapeutic agents do not efficiently direct to and accumulate in the desired sites due to their nonspecific distribution throughout the body. As a result, conventional therapeutic agents are required in high doses[4]. Moreover, drug discovery and development involves highly challenging, laborious and expensive processes. Unless, a minor change is imparted to an already marketed dosage form all other new formulations need to go through certain set of clinical investigation before it is released in the market. This process is highly costly and time consuming but must be understood as inevitable for the safety of the patient. The development process of each new drug takes an average of 15 years with an estimated cost of about US $ 0.802 billion. However, most of the drugs fail to achieve favorable clinical outcomes in the clinical phase, because they do not have the ability to reach the target site of action, or do not comply with the standards. Thus, the optimization of the drug molecules for achieving a plasma drug concentration associated with a safe clinical effect is the major challenge in drug development[2, 3].

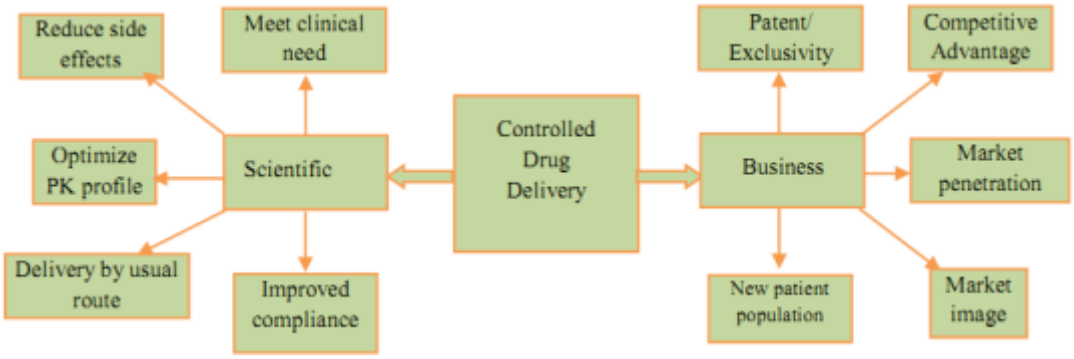

Figure 1.1 Strategic tools for drug delivery systems

An effective approach to overcome this critical issue is the development of controlled drug delivery systems of already available drugs. This could increase patient compliance and therapeutic efficacy of pharmaceutical agents through improved pharmacokinetics and bio distribution[5]. Therefore, delivering drug at controlled rate, targeted delivery are very attractive ways and being pursued very vigorously. Although conventional drug delivery formulations have contributed greatly to the treatment of disease, the development of controlled delivery systems has escalated[6]. Figure 1.1 illustrates the strategic tools for controlled drug delivery systems.

Controlled drug delivery systems offer numerous advantages compared to conventional dosage forms[6,7]. The benefit characteristics of controlled drug delivery systems are as follows:

- Controlled delivery of active agent at predetermined rate
- Reduced dosing frequency
- Better patient convenience and compliance
- Reduced GI side effects
- Improved efficacy/safety ratio
- Less fluctuating plasma drug levels
- More uniform drug effect
- Reduction in adverse side effects
- Lesser total dose

In order to achieve most effective drug therapy, it is required to have desired pharmacological response at the target without harmful side effect at other sites. This requires the correct dose of drug to be absorbed into the body and transported to the target[8]. The way in which a drug delivered to the target can have a significant effect on its efficacy. Some drug molecules have an optimum concentration range within which maximum benefit is derived, and concentrations above or below optimum range can be toxic or yield no therapeutic benefit at all (Figure 1.2) . More recently, there has been increasing interest in developing methods where drug release can be controlled either by an interaction between a “smart” material and changes in its environment. Ideally, such systems could determine the timing, duration, dosage, and even location of drug release[9].

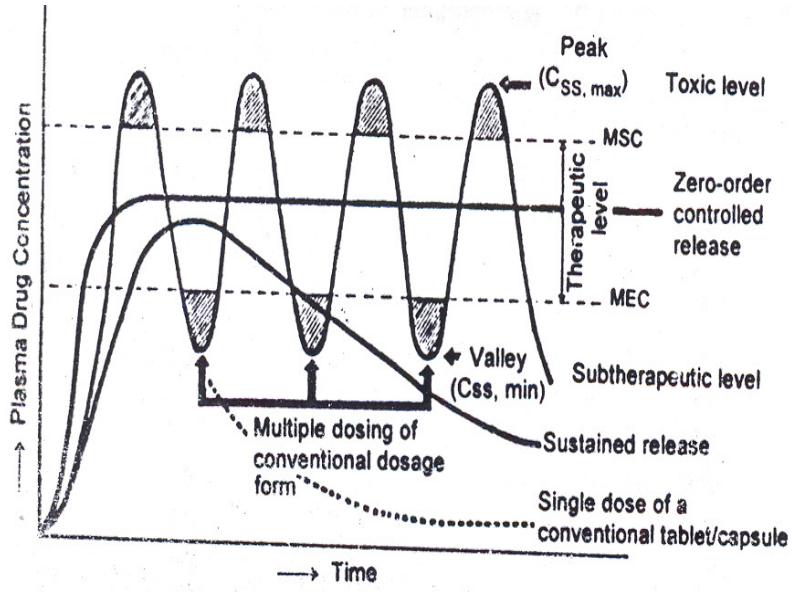

Figure 1.2 Drug level in the blood with controlled release delivery. (Biopharmaceuitics & pharmacokinetics D M.Brahmankar & Sunil B. Jaiswal)

Novel technologies with improved performance, patient compliance, and enhanced quality have emerged in the recent past. Oral fast-dispersing dosage forms, three-dimensional Printing (3DP) and electrostatic coating are a few examples of a few existing technologies with the potential to accommodate various physico-chemical, pharmacokinetic and pharmacodynamic characteristics of drugs[10]. The gastrointestinal tract is complex structure. A diagram of the gastrointestinal tract, outlining some of the key structures involved in and key physiological parameters that affect oral drug absorption (Figure 1.3). In order to gain an insight into the numerous factors that can potentially influence the It can be seen from this that the rate and extent of appearance of intact drug in the systemic circulation depends on a succession of kinetic processes. The slowest step in this series, which is known as the ***rate-limiting step,*** controls the overall rate and extent of appearance of intact drug in the systemic circulation. The particular rate-limiting step will vary from drug to drug. For a drug which has a very poor aqueous solubility the rate at which it dissolves in the gastrointestinal fluids is often the slowest step, and the bioavailability of that drug is said to be ***dissolution-rate limited.*** In contrast, for a drug that has a high aqueous solubility its dissolution will be rapid and the rate at which the drug

crosses the gastrointestinal membrane may be the rate-limiting step ***(permeability limited***[11].

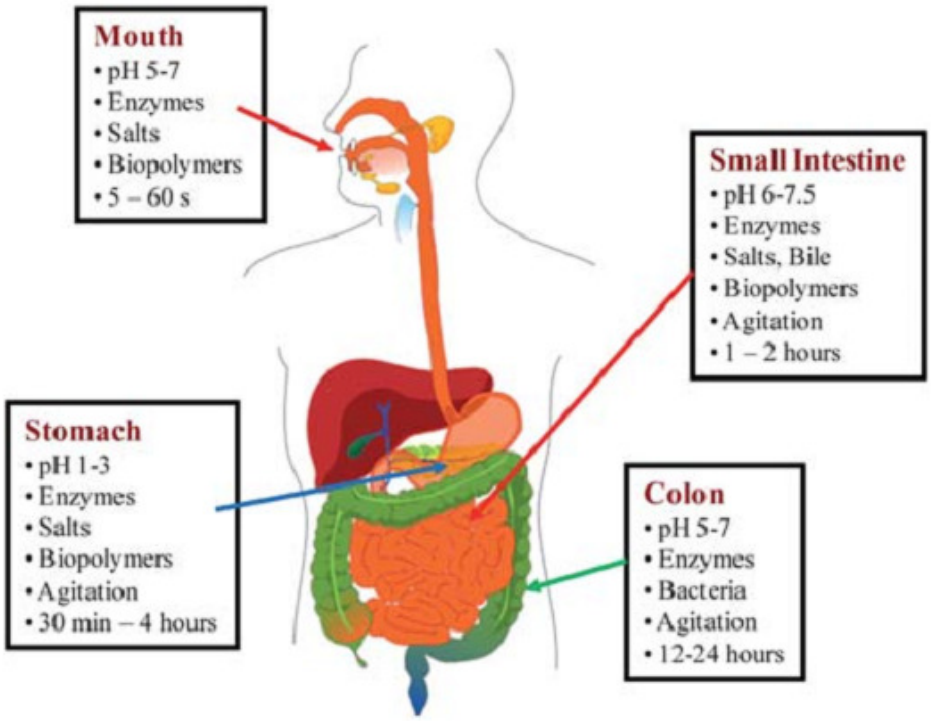

Figure 1.3 Diagram of the gastrointestinal tract, outlining some of the key structures involved in and key physiological parameters that affect oral drug absorption

Drug delivery has been accomplished by many conventional drug delivery systems. Oral drug delivery has been known for decades as a widely used route of drug administration. It has been envisaged as different dosage forms and designs. Oral route also brings with it the ease of administration, high patient compliance, and flexibility in design of the dosage form. The basic goal of any drug delivery system is to steady state blood, tissue level of the drug enough to mitigate/cure the disease taking the precaution of not being toxic to the body. The oral route of delivery is by far the most popular, mainly because it is natural and convenient for the patient and because it is relatively easy to manufacture oral dosage forms. Oral dosage forms do not need to be sterilized, are compact, and can be produced in large quantities by automated machines[11]. Therefore, foremost requirement of the drug delivery system is to identify orally active candidates that would provide reproducible and effective plasma concentrations *in vivo*[12]. The oral drug

delivery is the largest and the oldest segment of the total drug delivery market (Figure 1.4) [13,14]

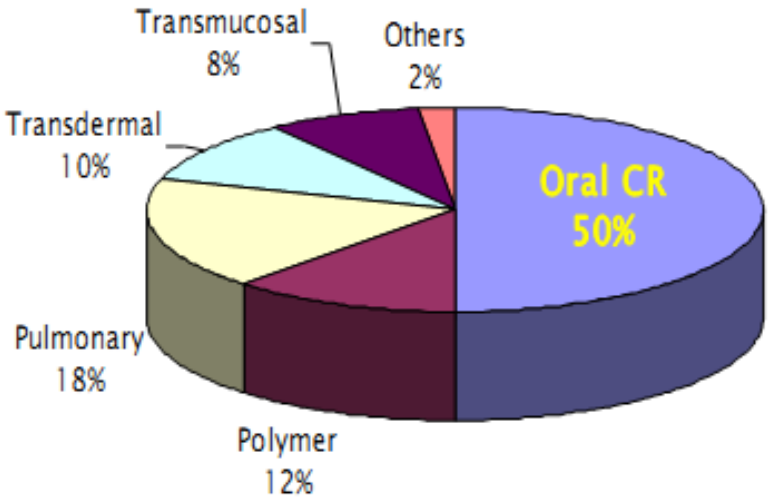

Figure 1.4 Current global business scenarios

1.3 Currently available drug delivery systems[15]

The carrier plays an important role in carrying the drug molecule to the target site. It acts as a skeleton or a back bone to the drug. Drug carriers are substances that serve as mechanisms to improve the delivery and the effectiveness of drugs. Drug carriers are used in sundry drug delivery systems such as:

- controlled-release technology to prolong in vivo drug actions
- decrease drug metabolism
- reduce drug toxicity

Carriers are also used in designs to increase the effectiveness of drug delivery to the target sites of pharmacological actions. The listed drug carriers have different physicochemical properties which make them suitable for different drugs. The common goal of the carrier is to transport drug molecules to the target site in a controlled manner. Ideally, they should be biocompatible, not cause any immunogenic or cellular reactions and

release drug molecule controllably at the target sites without altering its therapeutic effects. Some of the most popular drug carriers are:

- Liposomes
- Micelle
- Dendrimers
- Polymer
- Carbon nanotubes
- Gold and Iron oxide nano particles
- Titanium dioxide
- Mesoporous Silica nanoparticles

1.3.1. Liposomes

Liposomes are spherical self-closed structures, composed of curved lipid bilayers, which enclose part of the surrounding solvent into their interior. The size of a liposome ranges from some 20 nm up to several micrometers and they may be composed of one or several concentric membranes, each with a thickness of about 4 nm. Liposomes possess a lipid bi layer as a result of this it has unique properties such as amphiphilicity, which make them suitable for drug delivery[16]. A schematic representation of a liposome is shown in Figure 1.5. The drug molecules can be loaded within the lipid bilayer or in the aqueous core or at the interface between them. Since the lipid is an essential biomolecule for most living tissues and has an amphiphilic nature, that is, ability to spontaneously self-assemble into a variety of microstructures, liposome is used widely as a temperature or pH-sensitive drug delivery vehicle particularly for cytotoxic anti-cancer drugs[17].

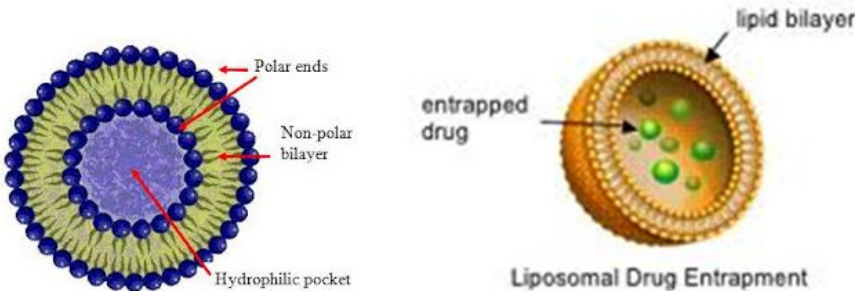

Figure 1.5 A schematic representation of a liposomes.

Hydrophobic drugs, for example, Amphotericin B, Taxol Orannamycin, can be passively incorporated into liposomes with 100% trapping efficiencies. For hydrophilic

drugs, however, active loading is required to get this level of entrapment[18]. Furthermore; the drug encapsulated in liposomes can be transported to the target site without rapid degradation and minimum side effect. Liposomes also have a unique ability to deliver the entrapped drug into cells by fusion or endocytosis, and therefore, any drug can be loaded into the liposome regardless of its solubility[19].

1.3.2. Micelles

Micelle is an aggregate of amphipathic molecules in water, with the nonpolar portions in the interior and the polar portions at the exterior surface, exposed to water. Amphiphilic molecules form micelle above a particular concentration which is called as critical micellar concentration (CMC)[20]. Micelles are known to have an anisotropic water distribution within their structure, means water concentration decreases from the surface towards the core of the micelle, with a completely hydrophobic (water-excluded) core. Hence hydrophobic drugs can be encapsulated/solubilized, into inner core. Consequently, the spatial position of a solubilized drug in a micelle will depend on its polarity, nonpolar molecules will be solubilized in the micellar core, and substances with intermediate polarity will be distributed along the surfactant molecules in certain intermediate positions. Polymeric micelles are generally more stable, with a remarkably lowered CMC, and have a slower rate of dissociation, allowing retention of loaded drugs for a longer period of time and, eventually, achieving higher accumulation of a drug at the target site. Furthermore, polymeric micelles have mesoscopic size range with a considerably narrow distribution. Size is certainly a crucial factor in determining their body disposition, especially when an enhanced permeation retention effect (EPR effect) is involved. It is also possible to functionalize the shell of the nanoparticles for targeted drug delivery[21, 22]. This technology is under clinical study for various applications some enlisted bellow in the table.

Product	Application	Company
Genexol PM	Non-small cell lung cancer	Samyang
Estrasorb	Estrogen therapy	Novavax
Medicelle	Cancer treatment	NanoCarrier
Flucide	Anti-influenza	NanoViricides
Basulin	Long acting Insulin	Flamel Technologies
DO/NDR/02	Palcitaxel delivery	Dabur Research Foundation
DDS-2001	Not disclosed	LaboPharm

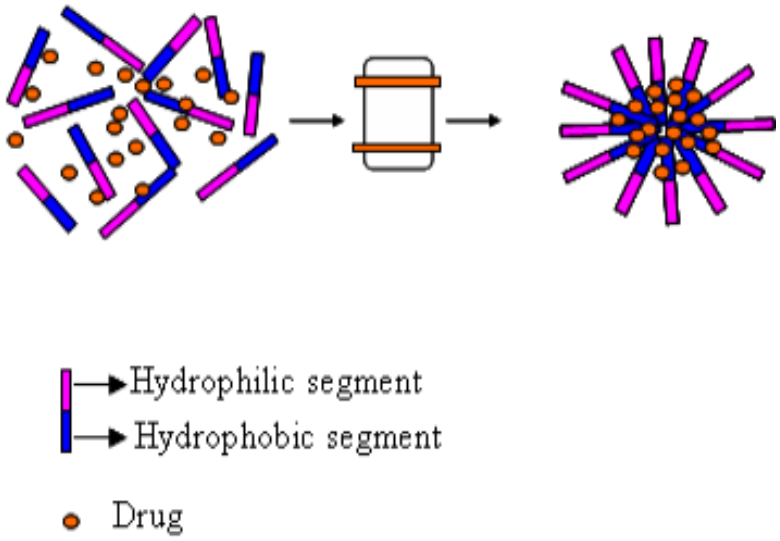

Figure1.6 Schematic representation for the formation of micelle by controlled dialysis of polymer and drug solution (in water miscible solvent)

1.3.3. Dendrimers

Dendrimers have a wide range of application that can be utilised in various areas such as material science, catalysis and drug delivery. This versatility to target multiple sites is because of the presence of branched structure which have wide scope as elucidated in Figure 1.6. Also, due to its distinctive structure, it can selectively host biomolecules and deliver them to the target sites. For example, the most common type of dendrimer is polyamidoamine dendrimers which can selectively host methotrexate[22]. However, the toxicity of dendrimers has been of concern. The non-degradable dendrimers produced side effects with repeated administration.Thus, the modification of cationic dendrimers is

essential to prevent its accumulation in the liver and to inhibit nonspecific toxicity. Polyester–based dendrimers are under research to overcome the biocompatibility issues faced by these polyamidoamine; which is done by bringing a change in the chemical composition[23].

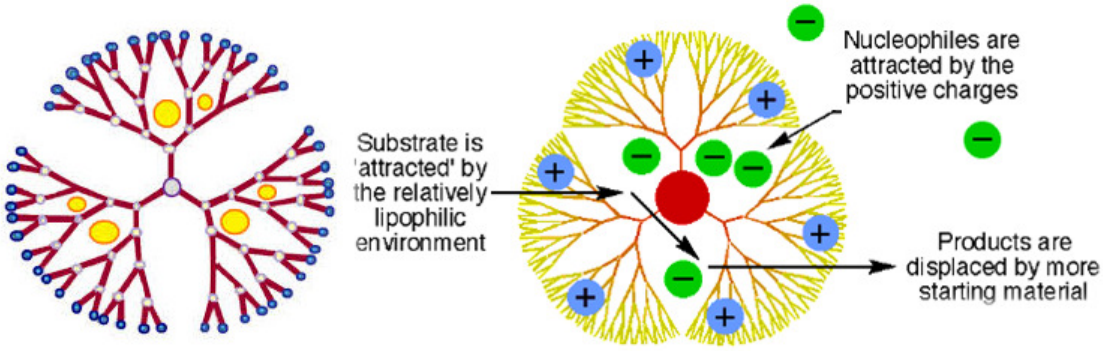

Figure 1.7 A schematic representation of a Dendrimers

1.3.4. Polymers

In addition to the widespread application of polymers in manufacturing different materials, they are also used in several formulations and devices for drug delivery. When developing drug delivery systems, it is important to control how much of the drug is being released – too much of the drug at once can be harmful to the body, but too little of it may limit its effectiveness. Delivery of drugs at the optimal dosage for optimal lengths of time will make them more effective and more powerful. It is with the use of polymers that manufacturers are able to deliver drugs more and more effectively. Some of the unique characteristics of polymers that make them versatile in drug delivery systems include :

- wide molecular weight distributions
- variety of visco-elastic properties
- special characteristics associated with phase transitions
- able to contract when heated
- variety of dissolution times
- specialized chemical reactivities
- tolerate a variety of manufacturing methods

Polymeric NPs are colloidal particles with a size range of 10–1000 nm, and they can be spherical, branched or core–shell structures. They have been fabricated using biodegradable synthetic polymers, such as polylactide–polyglycolide copolymers,

polyacrylates and polycaprolactones, or natural polymers, such as albumin, gelatin, alginate, collagen and chitosan. Advances in polymer science and engineering have resulted in the development of smart polymer (stimuli-sensitive polymer), which can change its physicochemical properties in response to environmental signals. Physical (temperature, ultrasound, light, electricity and mechanical stress), chemical (pH and ionic strength) and biological signals (enzymes and biomolecules) have been used as triggering stimuli. The versatility of polymer sources and their easy combination make it possible to tune up polymer sensitivity in response to a given stimulus within a narrow range, leading to more accurate and programmable drug delivery.

Polymeric nanocarriers can be categorized based on three drug-incorporation mechanisms. The first includes polymeric carriers that use covalent chemistry for direct drug conjugation (e.g., linear polymers). The second group includes hydrophobic interactions between drugs and nanocarriers (e.g., polymeric micelles from amphiphilic block copolymers). Polymeric nanocarriers in the third group include hydrogels, which offer a water-filled depot for hydrophilic drug encapsulation.

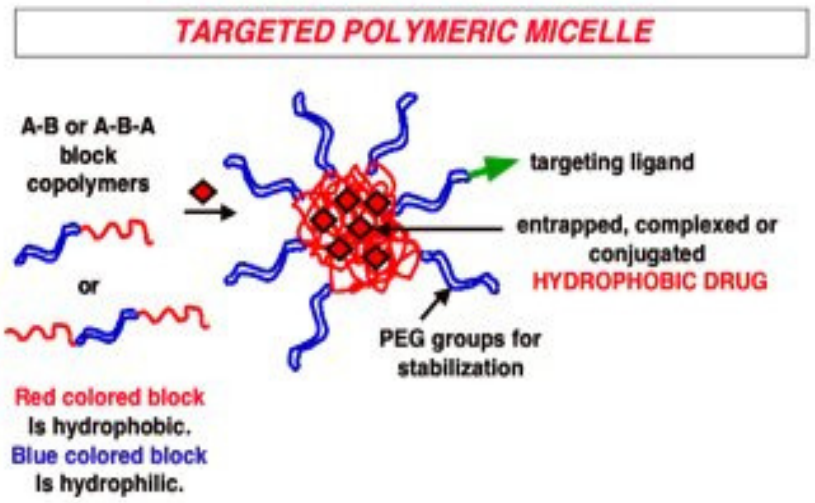

Figure 1.8 Polymeric micelles are used in delivering hydrophobic drugs more effectively. (Diagram courtesy of AS Hoffman, University of Washington, Seattle, WA.)

1.3.5. Carbon nanotubes[25,26]

Carbon nanotubes (CNTs) are very prevalent in today's world of medical research and are being highly researched in the fields of efficient drug delivery and biosensing methods for disease treatment and health monitoring. Carbon nanotubes technology has shown to have the potential to alter drug delivery and biosensing methods for the better, and thus, carbon nanotubes have recently garnered interest in the field of medicine. They are low dimensional sp^2 carbon nanomaterials, and their flexibility is produced by their various physicochemical properties that can be used in the transportation of various therapeutic agents such as vaccine, protein, antibiotics and anti-cancer and anti-inflammatory agents . A schematic picture of a CNT is shown in Figure 1.9. However, the insolubility of CNTs can pose health complications. For example, CNTs without functionalisation can accumulate in the lungs, which leads to pulmonary toxicity and inflammation. This perniciousness is highly dependent on material preparation and administration route of CNTs. As with liposomes and dendrimers, a biocompatible coating such as PEGlyation can remarkably reduce in vivo toxicity of CNTs.

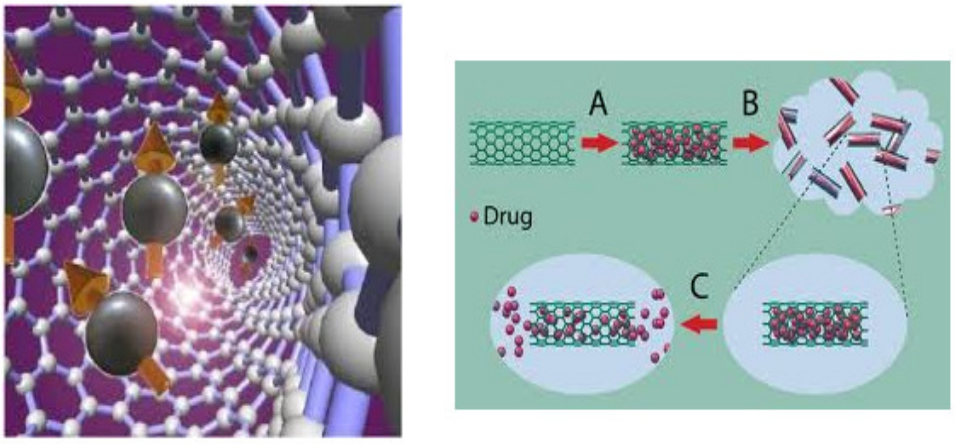

Figure 1.9 A schematic representation of a carbon nanotubes

1.3.6. Gold and Iron oxide nanoparticles

Gold and iron oxide are widely used in controlled drug release, especially in anti-cancer therapy. They are mostly used in combination with other biomolecules. For example, magnetic iron oxide provides the core of the particle, while the shell is composed of silica, dextran or gold attached via cross-linkers[27]. The advantage of using gold

nanoparticle is that it can release drug molecule in a controlled manner by absorbing heat and increasing kinetic energy to release drug molecules. Similarly, controlled release of drug molecule is possible with iron oxide under the influence of an external magnetic field. This can ultimately reduce dose and systemic absorption of cytotoxic drugs by guiding them to the target tumour cells[27]. However, in real practice, there are many parameters to be considered such as magnetic properties, field strength and field geometry, depth of target, blood flow, body weight and vascular supply. For gold nanoparticles, the accumulation and excretion profiles are not well understood, and the accumulation within bloodstream can block blood flow. Also, the cost of gold nanomaterials needs to be considered. Iron oxide needs surface functionalization due to poor solubility[28]. A schematic picture of a gold and iron oxide nanoparticle is shown in Figure 1.8.

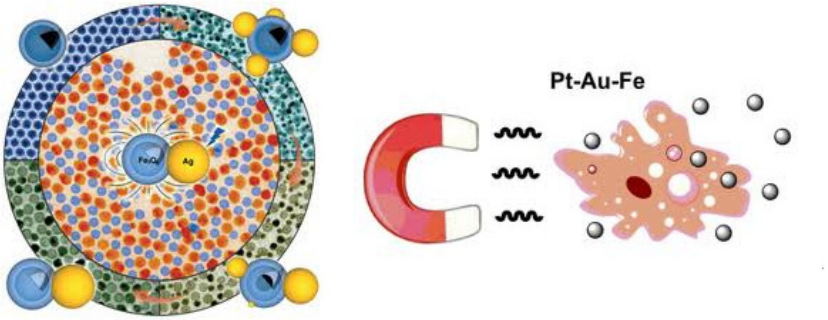

Figure 1.10 A schematic representation of a gold and iron oxide nanoparticles

1.3.7. Titanium dioxide

Micro- and nanoporous titanium dioxide (TiO_2) film, applied on the surface of titanium implant using micro-arc oxidation and anodic titanium oxide treatments, respectively, has been employed as a container for antibiotic loaded sol-gel derived silica xerogel. The presence of micro- and nanoporous TiO_2 film enhanced the drug-loading efficiency of sol-gel derived silica xerogel and provided controlled release of antibiotic. TiO_2 is also a potential photosensitiser, which can catalyse DNA damage; the release of drugs or active molecules can be triggered by ultraviolet light or X-ray radiation. TiO_2 is chemically inert and is ideal for use in chemo-therapy as it can inhibit tumour growth[29]. Recently, the development of 'smart' pH-responsive drug delivery vehicle based on TiO_2 nanoparticles for intelligent and enhanced delivery of chemotherapeutic drug has been

attempted. The 'smart' TiO_2 nanoparticles only release the anti-cancer drug under acidic pH, that is, in the vicinity of the tumour tissue, and this is a desirable characteristic for tumour-targeted drug delivery[30].

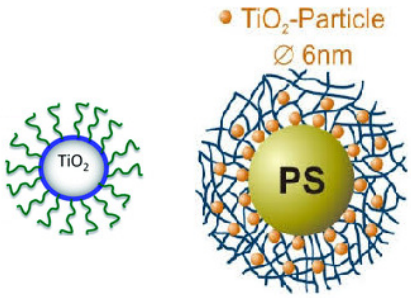

Figure 1.11 A schematic representation of a titanium dioxide nanoparticle

1.3.8. Mesoporous silica nanoparticles (MSNPs)

Ordered mesoporous materials have been preferred by many researchers due to their exclusive properties; highly ordered structure, tunable pore size, high surface area and good thermal stability. Moreover, these mesoporous materials have concerned for many applications such as; sensors, adsorption, catalysis and ion exchange. Even though these types of materials have used for many applications, they were not attracted for drug delivery systems until 2001. Today, intensive researches are ongoing to increase applications of ordered mesoporous materials in controlled drug delivery systems[31].

Mesoporous materials also get attention for drug delivery systems due to their biocompatibility. Mesoporous materials are biocompatible and nontoxic. Sarah P. Hudson and her coworkers did some experiments with animals to control the biocompatibility of mesoporous samples by using both SBA-15 and MCM-41 samples. They exhibited that mesoporous silicate particles had biocompatibility. Besides, nontoxic properties of mesoporous silicates were specified[32]. Mesoporous silica seems to be ideal for encapsulation of pharmaceutical drug, proteins and other biogenic molecules due to its following properties.

- An ordered pore network
- High pore volume
- High surface area
- A silanol-containing surface

Due to the presence of a high concentration of silanol groups on the surface (Figure 5), silica can be functionalized to control pore size and surface properties, which makes them suitable for controlled drug delivery [33].

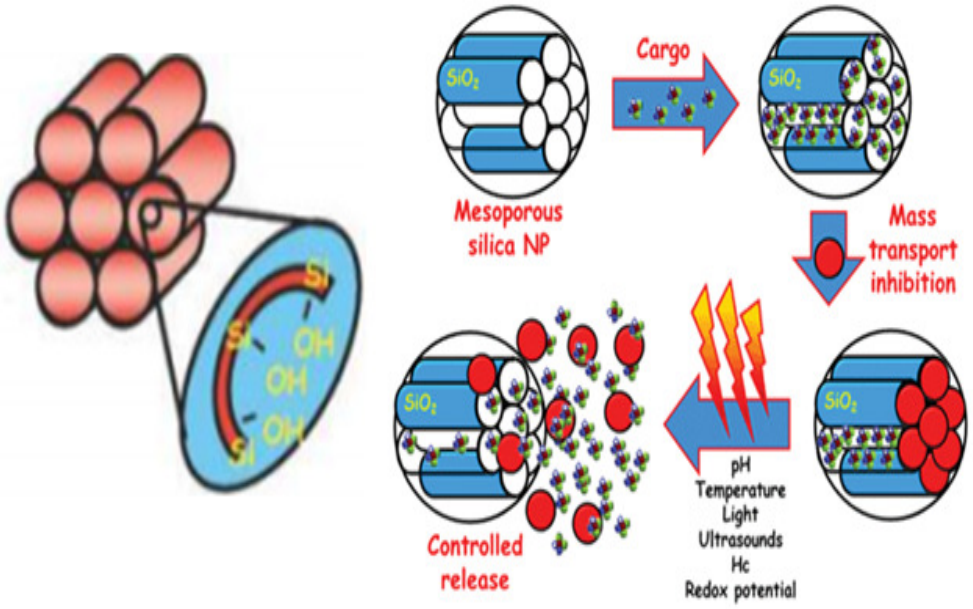

Figure 1.12 Nanostructured mesoporous silica matrices and a schematic representation of the different steps involved in the performance of MSNPs as stimuli-responsive drug delivery devices.

Many of the conventional nano drug delivery systems (DDS) (e.g. liposomes, micelles, and polymer-based) have reached the later stages of development, and a few have even received FDA approval. Over the last two decades, the development of synthesis and characterization techniques has blossomed for engineered new materials, including the ability to manipulate molecules and supramolecular structures for beneficial functions. This has led to the emergence of new DDS, such as inorganic delivery systems, for therapeutic and/or diagnosis purposes.1–4 Compared to the conventional DDS, most inorganic-based

DDS (e.g. mesoporous silica nanoparticles, MSNP) are still in their pre-clinical stages of development, with a few exceptions. The inorganic DDS which have reached the furthest stages of clinical trials are gold nanoparticles (GNP) used in drug delivery and hyperthermia based treatments. Figure.1.13 shows the leading nanocarriers for drug delivery and their general stages of development. The top row shows the representative conventional nanocarriers such as liposomes, micelles, dendrimers, and polymers. The bottom row shows novel inorganic nanocarriers such as carbon nanotubes, quantum dots, iron oxide, gold, and mesoporous silica nanoparticles

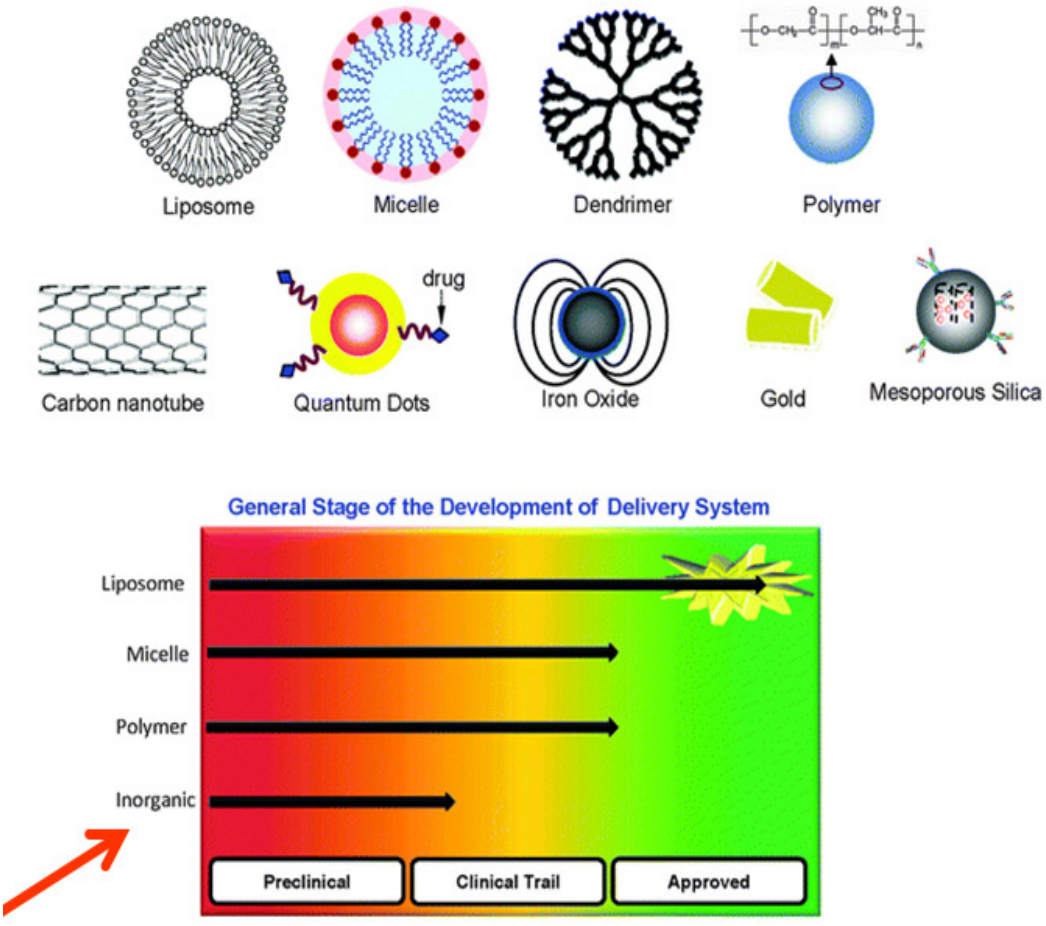

Figure 1.13 The scheme shows the leading nanocarriers for drug delivery and their general stages of development . The top row shows the representative conventional DDS. The bottom row shows novel inorganic nanocarriers[34].

1.4 Inorganic porous material for drug delivery

Inorganic porous carriers have an organized porous structure, which provides them with large inner surface areas (up to ~1800 m^2/g for MSNs like MCM-41, SBA-15) high surface to volume ratios, large pore volumes (reaching values as high as 1.7 cm^3/g for bimodal mesoporous silica-based spheres and 2.48 cm^3/g for SBA-15) tailorable and uniform pore sizes and well known possibilities of pore-wall functionalization allowing them to host in their interior a wide variety drugs and molecules of interest. That large inner surface area allows for the adsorption of large amounts of drugs or biomolecules because adsorption is a surface-based phenomenon. Also, these structured porous materials can be config-ured as micro- and nanoparticulated systems, fibers, monoliths, coatings, etc. opening up their application in diverse medical fields.

The International Union of Pure and Applied Chemistry (IUPAC) classifies porous materials accord-ing to their pore sizes into three categories, namely microporous (with pores below 2 nm), mesoporous (with pores between 2 and 50 nm), and macroporous (with pores above 50 nm)[35]. Examples of porous materials are depicted in Figure1.14.

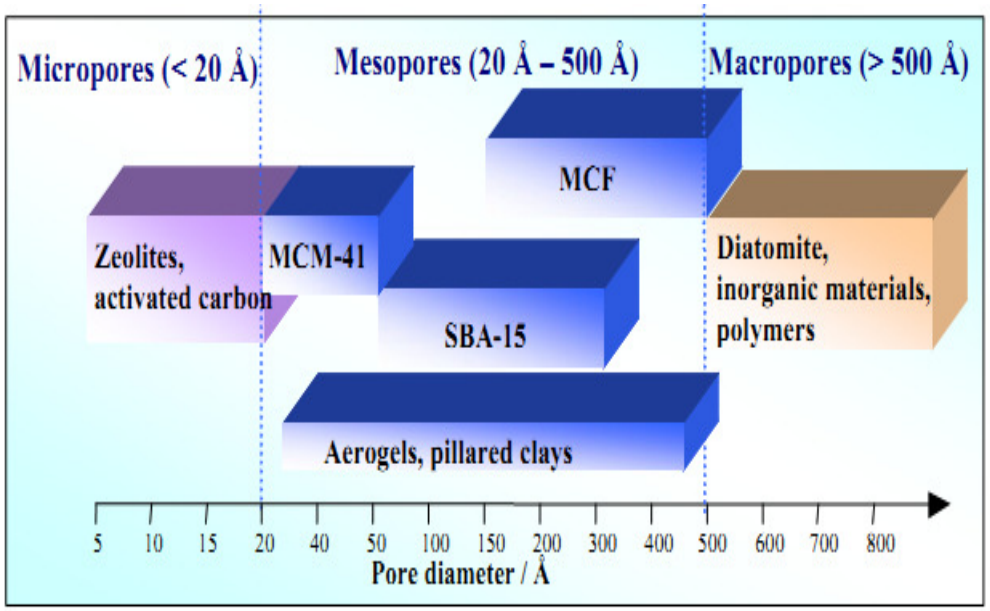

Figure 1.14 Schematic diagram of porous materials classification by IUPAC with examples of porous materials.

Porous materials are widely used in the industry principally in petrochemistry, catalysis, selective separations, storage, as electrode materials, as insulation, and in sensors and actuators. Porous structures can be organic, inorganic, or hybrid organic–inorganic com-posites. Both attributes together, size and nature, are taken into account when designing a drug carrier for delivery applications. The main advantages of using a structured porous material in drug delivery applications are:- (schematized in Figure 1.15)

Advantages of inorganic porous materials as drug carriers

- Large surface areas together with their large pore volumes have been used to improve the solubility of poorly soluble drugs.
- Low density allows them to float in the gastrointestinal tract and prolongs the gastric retention of oral drugs.
- Easy surface functionalization allows their grafting with bioadhesive and targeting moieties, and their interior pore volume protects biological payloads from physiological degradation.
- Hydrophilic character and porous structure can in principle be tailored to control the diffusion rate of an adsorbed or encapsulated drug, gene, or protein.
- They are resistant to microbial attack.
- They posses high chemical and mechanical stability under an array of physiological conditions.
- They act as a volumetric reservoir (i.e., nanotubes, nanocapsules) also as a diffusion controlling porous membrane or coating in drug-eluting devices (i.e., implants, needles).

- They can float in the gastrointestinal tract.
- They can adhere to different biological systems.
- Organized porosity has been used to achieve a sustained, controlled, or pulsed release in drug delivery applications.

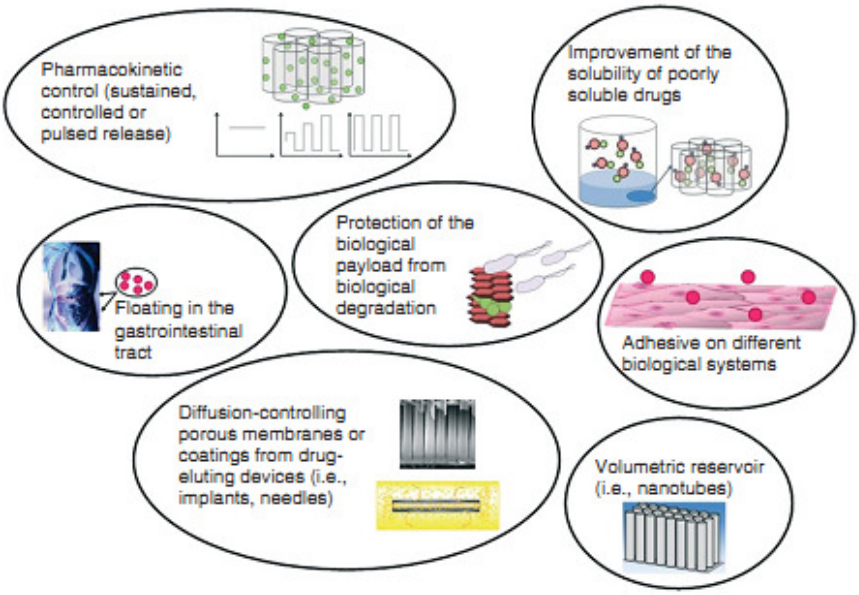

Figure 1.15 Schematic overview of some of the advantages described for porous materials in drug delivery applications[36].

When compared to the properties of conventional and other inorganic nanocarriers, MSNP have emerged as intermediary nanocarriers in the sense that they possess similar biocompatibility as conventional nanocarriers as well as the durability and versatility of inorganic nanocarriers. The intrinsically low toxicity of MSNP differentiates it from many other inorganic nanomaterials including other forms of silica-based nanomaterials such as fumed silica and nano quartz that are associated with poor biocompatibility and toxicity due to their highly reactive surface. (Detailed explanation given section 1.3.8)

1.5 Aerogels as a drug carrier

Besides their high surface area, pore structure and low density, being biocompatible, makes silica aerogel an ideal candidate for a varieties of life science applications. Silica aerogel were firstly used in 1960s as an additive for cosmetics and toothpaste under the name of Monsant's aerogels. The production has lasted for few years until silica aerogel was replaced by the cheap fumed silica. During the following decades aerogel production has been continuously improved resulting in spectacular properties and in the same time the cost factor was slowly minimized. In spite the cost factor, silica aerogel is chemically identical with fumed silica; the later has been proven to be used for pharmaceutics and food industry (Degussa, 2001), furthermore, silica aerogel characterized with higher surface area (1000 m^2/g) than that of fumed silica (200 m^2/g). These factors derive scientists to investigate silica aerogel as a carrier system for different active compounds. However, it should be mentioned that a complete toxicity investigations on silica aerogel are not available. In principle, active compounds can be loaded on silica aerogel matrix following two main routes: Mixing the active compounds drug with the sol before the gelation takes place, followed the drying step; (2) post treatment of the aerogel in a way that allows the deposition of the active compound particles on aerogel surface.

The stability and release kinetics of the active substance can be significantly improved by loading of drug into the aerogel. Thus, the materials based on aerogels have a great potential in the pharmaceutical, biomedical and many other fields. For certain active substances in the aerogel matrix, it was shown the increase of the relative bioavailability as compared to their crystalline form more than twice. Because of some properties of aerogels, for example: different nature, the specific surface area and average pore size - the best choice for of the active substance for a certain matrix.

An additional advantage compared with the nanoparticles is the fact that the drug particles being adsorbed or crystallized in the solid aerogel matrix have a lower tendency to agglomerate and are better protected from the environment. Other than surface area, the hydrophilic silica aerogel rapidly collapses in water. The reason for this collapse is the capillary forces which are exerted by the surface tension when liquid water enters a nanometre-scale pore of the aerogel. As a result, the solid silica backbone is fractured

completely and the aerogel loses its solid integrity. So the drug molecules adsorbed as single molecules on the aerogel network are immediately surrounded by water molecules, and thus dissolve faster [37]. Various drying techniques such as super critical drying, freeze drying, ambient pressure drying techniques are used of which super critical drying uses carbon dioxide liquid form as the solvent. Naturally it's a expensive technique and for large scale commercial production plans such routes of production must be avoided. Ambient pressure drying suits well for large scale production[38]. aerogel microspherical particles are produced using supercritical extraction of a gel-oil emulsion. Water in oil emulsion was produced by mixing the sol (dispersed phase) with a vegetable oil (continuous phase) followed by the gelation of the aqueous phase. The size and shape of the gel particles was controlled by the agitation (agitator shape and speed). The gel-oil emulsion was subsequently extracted with supercritical CO_2. Silica aerogel spherical microparticles with a surface area of 1100 m^2/g and mean particle diameters ranging from 200 µm to few millimeters were produced. The resultant aerogel particles were loaded with a model drug and coated with different polymeric materials in a spouted fluidized bed. The corresponding polymers were sprayed as aqueous solution or melts and the coating conditions (coating material, nozzle position, air flow rate, temperature etc) were optimized accordingly. Drying of the coated aerogel was achieved by heating the bed with a hot air stream. The physical, structural and release properties of the resulting formulations were evaluated. This technology allows providing specific release mechanism of pharmaceuticals[39].

1.6 Functionalized porous materials for controlled drug delivery

In recent years, mesoporous silica materials have been considered to be excellent candidates as carriers for drug delivery. On the one hand, textural properties of mesoporous silica increase the loading amount of drugs by hosting them within pore channels. On the other hand, the silanol containing surface can be easily functionalized, allowing for a better control over the drug diffusion kinetics.19,20 In addition, multifunctional mesoporous silica composites with excellent magnetic and/or luminescent properties represent another grand challenge for drug delivery targeting and tracking[40]. For normal aerogels , there exist only silanol groups on the channel walls, and these silanol groups simply form weak

intermolecular hydrogen bonds with drugs; hence, they are not strong enough to hold drugs and allow them to be released in a sustained manner. The need to synthesize suitable carriers to have specific host-guest interactions with drugs led us to introduce functional groups on the surface of SBA-15. It has been reported that the organic functionalization of SBA-15 can be achieved via two different routes, i.e., one-pot synthesis (or co-condensation)[41,42] and postsynthesis (or silylation)[43-45].

The method aims to enhance the loading of drugs in aerogels by means of surface functionalization of the carrier, and to investigate the influence of surface functional group on the release rate of the loaded drug in aqueous media. Aminogroups are an example of functional groups. Different approaches are followed to control the surface functionalization: pretreatment of the gel before the drying step, or a post treatment of the aerogels. The obtained amino-functionalized aerogels can be characterized by NMR and BET analysis, and UV-spectroscopy. It has been seen that the functionalized aerogels maintain the same structural properties as the origin aerogels[46].

1.7 Anti plateletic property of Aspirin

In addition to its effects on pain, fever, and inflammation, aspirin also has an important inhibitory effect on platelets in the blood. This antiplatelet effect is used to prevent blood clot formation inside arteries, particularly in individuals who have atherosclerosis (narrowing of the blood vessels) of their arteries, or are otherwise prone to develop blood clots in their arteries.

Antiplatelet agents are medications that block the formation of blood clots by preventing the clumping of platelets. There are three types of antiplatelet agents:

1. Aspirin,
2. Thienopyridines, and
3. Glycoprotein IIb/IIIa inhibitors.

These agents differ in the way they work, their potency (how strongly they prevent clumping), how rapidly they work, and their cost.

Aspirin

Aspirin prevents blood from clotting by blocking the production by platelets of thromboxane A-2, the chemical that causes platelets to clump. Aspirin accomplishes this by inhibiting the enzyme cyclo-oxygenase-1 (COX-1) that produces thromboxane A-2. While other NSAIDs also inhibit the COX-1 enzyme, aspirin is the preferred NSAID for use as an antiplatelet agent because its inhibition of the COX-1 enzyme lasts much longer than the other NSAIDs (aspirin's antiplatelet effect lasts days while the other NSAID's antiplatelet effects last only hours).

Thienopyridines

In addition to thromboxane A-2, platelets also produce adenosinediphosphate (ADP). When ADP attaches to receptors on the surface of platelets, the platelets clump. The thienopyridines, for example, ticlopidine (Ticlid) and clopidogrel (Plavix), block the ADP receptor. Blocking the ADP receptor prevents ADP from attaching to the receptor and the platelets from clumping.

Glycoprotein IIb/IIIa inhibitors

The glycoprotein IIb/IIIa inhibitors, such as abciximab (Reopro) and eptifibatide (Integrilin), prevent clumping by inhibiting a different receptor on the surface of platelets, the receptor for glycoprotein IIb/IIIa. The glycoprotein IIb/IIIa inhibitors that are approved by the FDA must be given intravenously (in the veins); which is difficult to administer in day to day life.

Since aspirin blocks only one of the several pathways by which platelet aggregation can occur, aspirin is a weak antiplatelet agent because platelet aggregation can be stimulated via another pathway.

Since glycoprotein IIb/IIIa inhibitors block the final common pathway for platelet aggregation (platelet aggregation is blocked regardless of the nature of the initial stimuli), glycoprotein IIb/IIIa inhibitors are the most potent antiplatelet agents. The maximal antiplatelet effect of glycoprotein IIb/IIIa inhibitors is approximately nine times that of aspirin.

The maximal antiplatelet effect of thienopyridines is in between that of aspirin and the glycoprotein IIb/IIIa inhibitors.

1.8 Mechanism of action

Suppression of prostaglandins and thromboxanes

Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the cyclooxygenase enzyme required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the PTGS enzyme. This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen), which are reversible inhibitors.

Low-dose, long-term aspirin use irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation. This antithrombotic property makes aspirin useful for reducing the incidence of heart attacks.[115] 40 mg of aspirin a day is able to inhibit a large proportion of maximum thromboxane A_2 release provoked acutely, with the prostaglandin I2 synthesis being little affected; however, higher doses of aspirin are required to attain further inhibition. [Tohgi, H; S Konno, K Tamura, B Kimura and K Kawano (1992).

Prostaglandins, local hormones produced in the body, have diverse effects, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Heart attacks are caused primarily by blood clots, and low doses of aspirin are seen as an effective medical intervention for acute myocardial infarction. An unwanted side effect of the effective anticlotting action of aspirin is that it may cause excessive bleeding.

COX-1 and COX-2 inhibition

There are two different types of cyclooxygenase: COX-1 and COX-2. Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. COX-2 normally produces prostanoids, most of which are proinflammatory. Aspirin-modified PTGS2 produces lipoxins, most of which are anti-inflammatory. Endothelial cells lining the

microvasculature in the body are proposed to express PTGS2, and, by selectively inhibiting PTGS2, prostaglandin production (specifically, PGI2; prostacyclin) is downregulated with respect to thromboxane levels, as PTGS1 in platelets is unaffected. Thus, the protective anticoagulative effect of PGI2 is removed, increasing the risk of thrombus and associated heart attacks and other circulatory problems. Since platelets have no DNA, they are unable to synthesize new PTGS once aspirin has irreversibly inhibited the enzyme, an important difference with reversible inhibitors.

Aspirin is readily broken down in the body to salicylic acid, which itself has anti-inflammatory, antipyretic, and analgesic effects. In 2012, salicylic acid was found to activate AMP-activated protein kinase, and this has been suggested as a possible explanation for some of the effects of both salicylic acid and aspirin[123][124]. The acetyl portion of the aspirin molecule is not without its own targets. Acetylation of cellular proteins is a well-established phenomenon in the regulation of protein function at the posttranslational level. Recent studies have reported aspirin is able to acetylate several other targets in addition to COX isoenzymes. These acetylation reactions may explain many hitherto unexplained effects of aspirin.

Aspirin – Its onset of action

When aspirin is given in low doses (50 mg/day), the complete inhibition of the COX-1 enzyme and hence maximal antiplatelet effect may take several days. At a dose of 160-325 mg/day, the maximal antiplatelet effect of aspirin occurs within 30 minutes. Thus, aspirin at low doses (75-150 mg/day) is used for the long term prevention of heart attacks and strokes, whereas moderate doses (160-325 mg/day) of aspirin are given in situations where an immediate anti-clotting effects are needed (such as in the treatment of acute heart attacks and unstable angina).

1.9 Role of aspirin in preventing and treating heart attacks and strokes

Aspirin is widely used either alone or in combination with other antiplatelet agents to prevent blood clots from forming in arteries. Aspirin is used specifically in several situations including:

1. Aspirin often is prescribed in moderate doses (160-325 mg/day) for patients who are having heart attacks to limit the extent of damage to the heart's muscle (by preventing blood clot formation in the blood vessels of the heart), prevent additional heart attacks, and improve survival.
2. Aspirin often is prescribed to patients undergoing surgery to open or bypass blocked arteries, including percutaneous transluminal coronary angioplasty (PTCA) with or without placement of coronary stents (CABG). Aspirin also is prescribed on a long-term basis to prevent clotting in the stents and/or the bypassed blood vessels.
3. Aspirin often is prescribed in low doses (50-160 mg/day) on a long-term basis to patients with prior heart attacks or strokes and to patients with TIAs (transient ischemic attacks or mini-strokes) and exertional angina to prevent heart attacks and ischemic strokes.
4. Aspirin may be used in low dose (50-160mg/day) for prevention of heart attack or stroke in patients with risk factors of these conditions including longstanding diabetes, vascular disease (previous heart attack or stroke, or poor circulation to the legs), or angina. Aspirin often is prescribed in moderate doses (160-325 mg/day) for patients who are having heart attacks to limit the extent of damage to the heart's muscle (by preventing blood clot formation in the blood vessels of the heart), prevent additional heart attacks, and improve survival.
5. Aspirin often is prescribed to patients undergoing surgery to open or bypass blocked arteries, including percutaneous transluminal coronary angioplasty (PTCA) with or without placement of coronary stents and coronary artery bypass surgery (CABG). Aspirin also is prescribed on a long-term basis to prevent clotting in the stents and/or the bypassed blood vessels.
6. Aspirin often is prescribed in low doses (50-160 mg/day) on a long-term basis to patients with prior heart attacks or strokes and to patients with TIAs (transient ischemic attacks or mini-strokes) and exertional angina to prevent heart attacks and ischemic strokes.
7. Aspirin may be used in low dose (50-160mg/day) for prevention of heart attack or stroke in patients with risk factors of these conditions including longstanding diabetes,

vascular disease (previous heart attack or stroke, or poor circulation to the legs), or angina.

8. Aspirin is prescribed in moderate doses (160-325 mg/day) to patients who are having unstable angina to prevent heart attacks and improve survival.
9. Aspirin is prescribed in moderate doses (160-325 mg/day) to selected patients who are having ischemic strokes to limit damage to the brain, prevent a second stroke, and improve survival.

Treatment of heart attacks

In a large multi-center study (Second International Study of Infarct Survival of the ISIS-2 trial) of patients having acute heart attacks, early treatment (within 24 hours of the onset of symptoms) with aspirin (160 mg/d) was found to reduce deaths from the heart attacks by 23%. The improved survival is believed to be due to aspirin's ability to quickly prevent further blood clots and the expansion of existing clots and thus limit the amount of damage to the heart's muscle.

Aspirin is easy to use, safe at the low doses used for its antiplatelet action, and fast acting. Aspirin at moderate doses (160-325 mg/day) produces an antiplatelet effect rapidly (within 30 minutes). The current recommendation is to give aspirin immediately to almost all patients as soon as a heart attack is recognized at a dose of 160-325 mg/d and to continue it for one month. The only reason for not using aspirin is a history of intolerance or allergy to aspirin or evidence obvious active bleeding (such as actively bleeding stomach ulcers).

Prevention of further heart attacks

There are two types of heart attack prevention, primary and secondary. Preventing the first heart attack is called primary prevention. Preventing further heart attacks among patients who already have had a heart attack is called secondary prevention.

Within six years after the first heart attack, 16% of men and 35% of women will have a second heart attack. Long-term, daily aspirin (75-325 mg/d) has been shown to reduce the risk of second heart attacks and improve survival among both men and women. Additionally, long-term secondary prevention with aspirin also has resulted in fewer

ischemic (lack of blood flow due to blockage in blood vessels from clot formation) strokes. Therefore, survivors of heart attacks usually take daily low dose (75 mg-160 mg/d) aspirin indefinitely to prevent further heart attacks as well as strokes.

Aspirin taken long-term is an important part but NOT the only measure for preventing heart attacks.

Prevention of strokes

Patients with prior strokes and TIAs (mini-strokes) usually have significant atherosclerosis of the carotid and /or the smaller arteries within the brain and are at risk of further strokes. (These patients often have coronary atherosclerosis as well and are at risk for heart attacks). Long-term low-to-moderate doses of aspirin (50-325 mg/d) have been found to reduce the risk of strokes as well as heart attacks in these patients.

Aspirin is not the only medication to prevent strokes among patients with atherosclerosis. Another anti-platelet agent, clopidogrel (Plavix), also has been used, especially in patients who are intolerant or allergic to aspirin. Aspirin is sometimes combined with a second anti-platelet agent, dipyridamole (Persantine, Aggrenox), to prevent strokes.

Antiplatelet agents are not the only measures that prevent strokes. For example, aspirin alone may not be sufficient to prevent embolic strokes in patients at risk for these strokes, such as in patients with atrial fibrillation. In these patients, warfarin (Coumadin), an oral anti-coagulant that is a stronger anti-clotting medication than aspirin, may be necessary.

In patients with ischemic strokes or TIAs who have advanced atherosclerosis and narrowing of the carotid arteries, carotid endarterectomy (a surgical procedure to widen the narrowed carotid artery, the main blood vessel feeding the brain) or the introduction of stents within the carotid artery may be necessary to prevent strokes. As described below, the recommendations for the secondary prevention (in people who already have had a heart attack or stroke) of future attacks are more compelling. An ideal dose of aspirin is one that maximizes its benefits but minimizes side effects. However, the ideal dose of aspirin for primary or secondary prevention of ischemic strokes and heart attacks has not been

established firmly. At lower doses, such as 50-75 mg/d, the antiplatelet effect of aspirin can be achieved in several days instead of minutes. Since the risk of serious bleeding from aspirin is lower at lower doses, 50-75 mg/d is an appropriate dose for long-term primary and secondary prevention. Even though aspirin at doses as low as 40 mg/d has been shown to have anti-platelet effects, there is insufficient and inconclusive data to show that such low doses are effective in preventing heart attacks and ischemic strokes.

The USPSTF also looked into the optimal dose of aspirin for primary preventive purposes in 2009. They concluded that the low doses of 50-100mg daily were as effective as higher doses in preventing vascular disease and less associated with bleeding complications.

Aspirin taken long-term is an important part but NOT the only measure for preventing heart attacks.

Prevention of strokes

Patients with prior strokes and TIAs (mini-strokes) usually have significant atherosclerosis of the carotid and /or the smaller arteries within the brain and are at risk of further strokes. (These patients often have coronary atherosclerosis as well and are at risk for heart attacks.) Long-term low-to-moderate doses of aspirin (50-325 mg/d) have been found to reduce the risk of strokes as well as heart attacks in these patients.

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Aspirin prevents blood clots from forming inside arteries affected by atherosclerosis, but aspirin does not prevent atherosclerosis. Other measures (losing excess weight, controlling high blood pressure and diabetes, lowering LDL cholesterol, increasing HDL cholesterol, and stopping cigarette smoking) are necessary to prevent atherosclerosis.

Most physicians these days recommend low doses of aspirin long-term for patients with advanced atherosclerosis for secondary prevention purposes. Such patients include those with:

- prior heart attacks
- prior strokes
- exertional and unstable angina
- TIAs (transient ischemic attack, mini-stroke)
- peripheral vascular disease (poor artery blood flow to the legs)
- vascular procedures such as PTCA and CABG

Doctors also consider low dose aspirin in patients at risk for atherosclerosis because they:

- Have high blood LDL cholesterol
- Are males over 45 or are postmenopausal or over 55 females
- Have high blood pressure (hypertension) after high blood pressure is controlled with medications
- Use tobacco
- Have diabetes mellitus
- Have a family history of coronary heart disease

2. REVIEW OF LITERATURE

Manuel Arruebo et al. [47] demonstrated the numerous possibilities of structured porous inorganic materials in drug delivery applications in their review. The focus of the current research in designing targeted drug delivery systems using inorganic porous materials was elucidated. It describes the use of porous inorganic materials such as mesoporous silicas, hydroxyapatites, tricalcium phosphates, aluminosilicates, mesoporous carbons, MOFs, porous silicon, PMO, calcium silicates, ceramic and carbon based nanotubes, and layered silicates numerous possibilities in the biomedical field.

Krajewski et al. [48] worked on hydroxyapatite and bio inert alumina as a porous source of drug delivery devices. Possibility to control pore size was taken into consideration. The release of the drug was carried out pharmacologically. This study allowed a plausible interpretation of the phenomena involved in releasing a substance with pharmacological activity and simple molecular structure from ceramic samples with different porosimetric intervals, preventively impregnated with that substance. They conclude it as a preliminary work targeted in preparing ceramic drug delivery systems. The dimensions of pore size distribution influence the degree of efficiency of release mechanism of drugs. Advantage of bimodal pores over monomodal porous system was elucidated for better drug release also pointing out the better combinations of size and amount of the two classes of pores.

Keji Yamamoto et al. [49] studied the adsorption and entrapment of salicylamide molecules into folded sheets of mesoporous (FSM-16). The study concluded that the heat treatment of the physical mixture of salicylamide with FSM-16 gives a solid dispersion in which drug molecules change to amorphous and adsorb into carrier; in turn showed good release**.** The adsorptive ability of FSM-16 micropores might promote the rapid adsorption of salicylamide. From the thermal analysis, it was found that the salicylamide adsorbed could exist in an amorphous state stably. It was revealed that the solid dispersion of salicylamide and FSM-16 was useful in achieving fast dissolution of salicylamide.

M. Vallet Regi et al. [50] studied MCM-41 as a potential source of drug delivery carrier. The disordered pores found on the surface of siloxane bridges and free silanol groups were studied. Also cited the two main factors that determine the drug loading i) Pore wall surface and ii) functional group present in the surface. Hence they performed functionalization as well as changing the drugs as separate trails in the study. XRD of both MCM-41 and amine modified MCM-41 shows how the functionalization of the pore wall does not affect to the structural order. This study evidences that the host-guest chemistry in MCM-41 materials can be conveniently manipulated as to fine the adsorption and delivery behavior of molecules of pharmacological interest.

Wei Zeng et al. [51] conducted experiments on MCM-41 materials by organic aminopropyl modification. Solvothermal process was adopted. Aspirin was utilized in the controlled drug delivery system. The release study was conducted and use of various aminopropyl groups on the pore wall was studied. Characterization carried out by XRD, TG, FTIR, TEM, UV. The results show that the release properties of this delivery system are affected by the amount of aminopropyl groups on the pore wall and the ordered structure of mesoporous materials, which indicates that appropriate organic functional groups and post-treated time are favorable for the drug delivery.

Kim et al. [52] reported composites of enzyme molecules and magnetite nanoparticles in hierarchically ordered, mesocellular, mesoporous silica via a ship-in-a-bottle approach. These two kinds of nanocomposites could respond well to a magnetic field, they had irregular article shapes and sizes. A Magnetically Separable, Highly Stable enzyme System Based on nanocomposites of enzymes and magnetic nanoparticles Shipped in hierarchically ordered, mesocellular, mesoporous silica.

S. Kawi et al.[53] Functionalized mesoporous SBA-15 with amino silane and resultant white solid was filtered off. The resultant functionalized materials were investigated for controlled drug delivery. The characterization studies were carried out with FTIR, N2 adsorption/desorption analysis, zeta potential, XRD, TEM etc. The drugs selected were Ibuprofen and Bovine serum albumin. Since, in-vitro dissolution testing is important for drug development and quality control, it has been used in this study to investigate the difference in the release rate of model drugs from SBA-15 samples into biological medium. The surface properties of functionalized SBA-15 materials have been shown to be tunably modified using two different routes, namely, one-pot synthesis and post synthesis Post synthesis technique was found to be most favorable for drug release that the one pot synthesis.

Qunli Tang et al. [54] conducted separate experiments on MCM-41 with and without surface modification. He found that those without modification released ibuprofen within an hour and when surface functionalization done with hexamethyldisilazane (HMDS). The release was 70% after 48 hours elucidating the controlled release nature; the amount of functionalization also determined the rate of release. The XRD pattern of the MCM-41 indicates a typical pattern for a hexagonally ordered MCM-41 with strong reflection peaks in (100), (110), and (200). The diffraction intensities of these corresponding peaks are markedly decreased for the MCM-41(ibuprofen loaded). This is likely due to the larger contrast in density between the matrixes and open pores MCM-41 relative to that between the matrix and ibuprofen filled in pores MCM-41(Ibuprofen loaded).

Hubert Koller [55] worked on producing self assemble silica and hybrid organosilica sol-gel materials. To it a pharmaceutically important Presantin was loaded. Larger pores and faster release were observed at weakly acidic range (pH 5.6) whereas, more dense materials and slow release at pH 2-3. The organically functionalized host gels can control drug release. To gain a deeper insight into the kinetics, ^{1}H and ^{29}Si NMR spectroscopy have been employed in situ on the reaction solutions of tetraethyl orthosilicate (TEOS) and

acetoxypropyltrimethoxysilane (ATS). The drug is closely surrounded by the gel matrix, leading to the inhibition of the release profile. Therefore, the fact that no nitrogen is adsorbed for these gels must be explained by N_2 diffusion blockage. The use of ATS side groups in an inorganic-organic hybrid gel leads to promising release properties. The porosity of the carrier gel shows a bimodal pore-size distribution as measured by positron annihilation lifetime experiments (PALS).

Rajendra Kumar et al. [56] elucidated the use of a novel hybrid nano structured sponge to conduct studies in the concept of oral delivery of peptides employing a model drug for loading insulin. The modified sponge was acid-base neutralized for hydroxyapatite and incorporating chitosan as the organic counterpart. The films showed good insulin loading and alginate could be coated on them so as to release the drug only on gastric and intestinal pH. The drug release can be rationalized as drug adsorbed on to the surface and into the nanoporous architecture. The proof of concept of using the organic- inorganic sponge of nano structured, non-toxic materials was apt to deliver a peptide drug, insulin was studied. *In vitro* release proved good in both the simulated body fluid and also simulated intestinal fluid for the test hypothesis.

Jesus Santa Maria et al. [57] synthesized metallic iron nano particle with micron sized mesoporous molecular sieves (MCM-41 and MCM-48). Several cycles of wet impregnation under vacuum, followed by drying, oxidation and reduction steps. These iron loaded hollow silica micro capsules showed magnetic moment of 2.4 emu/g after 3 cycles and coercivity. The wet impregnation technique was used to load iron within the structure of the prepared powder (particles) and microcapsules. In a typical procedure, the air contained within the pores and cavities of these materials was first removed under vacuum, and then, 1.6 M $Fe(NO_3)_3.9H_2O$ solution was admitted into the vessel to carry out impregnation at atmospheric pressure. It was inferred from the study that because of the high volume of their internal cavities, the microspheres are capable of delivering a higher

drug load. Both groups of materials (MCM-41 and MCM-48) can therefore be considered as very promising materials for application in drug delivery.

Maria Vallet-Reji et al. [58] addressed the growing interest towards using MCM-41, SBA-15, and MCM-48 as potential drug delivery carriers. Introduction of other metal-organic frameworks have also been postulated for the same. The drug incorporation is commonly carried out by soaking of the matrix in a highly concentrated drug solution and subsequent drying. Therefore, the process is mainly based on the adsorptive properties of mesoporous materials. They also proposed the application could be extended towards bone implants citing these materials as a potential bioceramic which can be concluded using biocompatibility studies of these functionalized materials which in turn act as stimuli-response systems. For certain applications, the delivery of adsorbed molecules needs to be modulated by environmental stimuli such as pH and temperature changes or light. Furthermore, many site-selective delivery systems, such as those for highly toxic antitumor drugs, require zero release before the targeted cells or tissues are reached. Current research is focused on the design of ordered mesoporous materials with certain functional groups that respond to environmental changes and thus modify the adsorption and release characteristics.

Shizhang Qiao et al. [59] reported a novel one step synthesis pathway that controls both functionality and morphology of functionalized periodic helical mesostructured silica by co-condensation of TEOS and organoalkoxysilane (hydrophobic) ones. The use of surfactants as templates was demonstrated. Thiol functionalized helical mesostructured silica was synthesized by the co-condensation of TEOS and MPTS using ^{16}CTAB or ^{18}CTAB as a surfactant, without the use of any additives. The amount of MPTS was varied from 0.0 to 0.1g to investigate its effect on the formation of the helical mesostructures. Helical mesostructures were formed with hydrophobic groups with surfactants and thereby formation of helical rod likes cylindrical micelle forming structures**.** The work is the first of its kind of a one-step synthetic pathway that can control both functionalities and

morphology of functionalized periodic helical mesostructured silica by the co-condensation of TEOS and hydrophobic organoalkoxysilane using achiral surfactants as templates. The morphology and pitch of the helical structure was controlled by the amount of organoalkoxysilane.

Lee et al. [60] reported synthesis of mesoporous silica nanoparticles (MSN) with different densities of positive charge. The positive charge brought about by the functionalization with trimethylammonium (TA). Colon related diseases such as irritable bowel syndrome, Crohn's disease, and ulcerative colitis could be more effectively treated when the therapeutic drugs are delivered to the colon tissue. Studies were carried out using Orange II a fluorescent tracer molecule and an anti-inflammatory prodrug sulfasalazine were used. Effects of environmental pH (from 1 to 10) on the adsorbed amounts of Orange II and sulfasalazine molecules onto MSN-TA samples were investigated. A pH-responsive controllable drug release system has been designed by the authors by incorporating positive charges in the framework of MSN so that anionic molecules can be efficiently adsorbed inside of the nano channels with minimal release under acidic pH value. The sustained release at pH 7.4 due to partial static negative charge development was explained targeting the intestine.

Ashish Datt [61] carried out his PhD on mesoporous silica and zeolites for drug delivery. Zeolites and mesoporous silica were used as drug delivery systems for the loading and release of small drug molecules, aspirin and 5-fluorouracil. Different parameters were varied such as aluminum content in the zeolite, effect of distribution of functional groups and the method of surface modification in case of mesoporous silica. The effect of the aforementioned variables was studied on drug loading and release from these microporous and mesoporous systems. The drug loaded materials were extensively characterized using various physical techniques such as powder X-ray diffraction, nitrogen isotherms, infrared spectroscopy, solid state NMR and thermo gravimetric analysis. Quantum calculations and molecular dynamics simulations were performed in

order to validate the experimental data and also to obtain a molecular level insight of the drugs inside the pores of the host materials. Drug templated synthesis of mesoporous silica was also carried out in the presence of aspirin as the template. The aspirin templated material was characterized by aforementioned techniques and showed a sustained drug release profile.

Tewodros Asefa et al. [62] showed that drug incubation temperature and methods which were employed removing surfactant template from mesoporous materials and the solvents used for surface functionalization also has a affect on the drug absorption and release properties. Rhodamine 6G and cisplatin anti cancer drugs were selected for studies on mesoporous silica (MCM-41 & SBA-15).The comparative studies of organic-functionalized mesoporous dependent on not ony the temperature but also the concentration. Study revealed the change in room temperature to 50^{o}C and 75^{o}C has a say on drug loading and drug release correspondingly. The experiments on cisplatin also confirmed the effect of temperature. The adsorption and release properties toward R6G and cisplatin of ethane-functionalized periodic mesoporous organosilica (ethane PMO) were also investigated. The ethane PMO was found to adsorb a higher amount of R6G than MCM-41.

Shizhang Qiao et al. [63] also carried out the work of magnetic nanoparticles coating on silica or polymers has been extensively applications explored in biomedical fields such as targeted drug delivery and magnetic resonance imaging. A pH-responsive controllable drug release system has been designed by incorporating positive charges in the framework of MSN so that anionic molecules can be efficiently adsorbed inside of the nanochannels with minimal release under acidic pH value. The particle size, shell wall thickness, and saturation magnetization value of periodic mesoporous organosilica magnetic hollow spheres are tunable by varying the amounts of fluorocarbon surfactant and magnetic nanoparticles. The pore surface properties can be adjusted by the co-condensation of BTME with functional silane precursor. The high saturation magnetization ensures that

these functional mesoporous hollow spheres become a very efficient protocol to targeted drug delivery assisted by magnetic fields.

Shefan Kaskel et al.[64] studied the synthesis of Rattle-type Fe_3O_4@SiO_2 hollow mesoporous spheres with large cavities using the colloidal carbon spheres as the templates. The spheres are well monodisperse and nearly uniform in dimension with particle size of ca. 900 nm. The thickness of the mesoporous silica shell is about 100 nm, and only one Fe3O4 particle of ca. 100 nm in diameter is encapsulated in each hollow mesoporous silica sphere. The magnetic measurement indicated that the Fe3O4@SiO2 hollow mesoporous spheres exhibited ferromagnetic behavior with the magnetization saturation of 1.6 emu/g. Using aspirin as a model drug, the Fe3O4@SiO2 hollow mesoporous spheres showed high drug loading capacity and sustained release property. Therefore, it was demonstrated that magnetic hollow mesoporous spheres provides a very promising candidate for application in a targeted drug delivery system.

Si-Xue Cheng et al. [65] studied the sustained release profile of Doxorubicin hydrochloride on the synthesized CaCO3/CMC hybrid microspheres and nanospheres. The characterization carried out by Scanning electron microscopy, FTIR, X-ray diffraction, TGA etc. High encapsulation and sustained release profile was seen from micro and nanospheres. By taking into account the SEM studies and other experiments envisaged the CaCO3 microparticles were prepared in the presence of highly nanoporous polysaccharides which provide a strong capability to load drugs. The drug (Doxirubicin hydrochloride) loaded microspheres were examined under the confocal microscope followed by DSC for the comparison of both blank and drug loaded micro / nanospheres. Drug loaded microspheres were immersed in physiological buffer solution. At predetermined intervals samples were taken and replaced with equal amount of the buffer solution and analyzed by UV-Visible spectroscopy.

Michelina Catouro et al. [66] worked on bringing out and characterize novel sol-gel organic-inorganic hybrid materials for controlled drug delivery applications based on

poly(ε-caproactone) PCL 6,12,24 &50 wt%) and zirconium-ytria ($ZrO2.5\%Y_2O_3$). This was done by using multicomponent solutions. Characterizations were done by FTIR, NMR. Release kinetics carried out in simulated body fluid and analyzed in UV-Visible spectroscopy for anti inflammatory drugs. The presence of hydrogen bonds between organic-inorganic components of the hybrid materials was suggested by Fourier transform infrared (FTIR) analysis, and strongly supported by solid-state NMR. A single-step, sol-gel process was then used to precipitate microspheres containing ketoprofen or indomethacin for controlled drug delivery applications. Release kinetics in a simulated body fluid (SBF) was subsequently investigated. The amount of drug released was detected by UV-VIS spectroscopy. Pure anti-inflammatory agents exhibited linear release with time, in contrast drugs entrapped in the organic-inorganic hybrids were released with a logarithmic time dependence, starting with an initial burst effect followed by a gradual decrease. Pure drugs showed linear release whereas inorganic-organic showed controlled one.

Timo Lebold [67] described how mesoporous materials act as an ideal drug delivery carrier in a drug delivery system. The tuning of pore size and its effect on drug binding property was also studied. The characterization was done using XRD and C^{13}-NMR. The release or diffusion dynamics studied and correlated diffusion coefficients to pore distance. This is the first time that fluorescence spectra of Doxorubicin in such diluted samples have been acquired. At high concentrations (from 10-2 mol/L down to 10-6 mol/L) the spectrum is blue-shifted with a major band at 600 nm. At a concentration of 10-7 mol/L the spectrum gets shifted to the red with a peak at 645 nm. This change in spectrum is attributed to aggregation. The dimerization process could lead to an increase of internal hydrogen-bonding with the oxygen atoms in the silica walls, reducing the attractive interactions between drug and host. The structurally related cytostatic Actinomycin D indeed aggregates to inverted dimers Pluronic P123 templated mesoporous films were loaded with Doxorubicin (Doxorubicin concentration in the synthesis solution 10^{-4} mol/L) in order to determine the drug release kinetics. The P123 templated structures were chosen for this experiment because Pluronic is well-known as biocompatible micellar nanocarrier for pharmaceuticals, such as Doxorubicin.

Robin H Bogner et al. [68] explained the use of mesoporous materials as amorphous drug delivery system. Attempts were made to study the interaction of crystalline compounds with mesoporous media. For this synthesis of various types of mesoporous silica were prepared**.** Because of the large surface area, complex surface chemistry, and heterogeneous surface structures, their interaction with a drug compound in a formulation is often different and more complex than a nonporous excipient. Method of preparing amorphous drug silica formulations was studied. Organic solvent was used to introduce drug compound to mesoporous silica. Drug was first dissolved in an organic solvent to form a concentrated solution. Using solvent impregnation method, the properties of organic solvents likely contribute to the efficiency of drug loading. The effect of a solvent is first discussed, followed by the *in vitro* and *in vivo* performances of amorphous formulations. The transformation mechanism of drug in the presence of mesoporous excipients can be rather advantageous in formulating and delivering poorly soluble compounds to achieve higher bioavailability.

Michael Froba et al. [69] explained the rise of a new class of materials; organic-inorganic hybrid materials. They utilized the two sides; inorganic part builds the robust substrate while organic part shows them for the number of ways the material can be used. The potential application in targeted drug delivery, magnetic resonance imaging etc were also explained. Highlighted part includes biocompatibility and biodegradability apart from high surface area, larger pore size and volumes. Some of the presented organosilica materials possess performances that are already superior in comparison to the conventional ones, for instance in the field of chromatography. The author concludes that the material possesses good property compared to conventional ones but cost effectiveness can be brought in to account only with large scale production.

Michela Signoretto et al. [70] synthesized pure and modified silica materials by using sol gel process. This was then implemented as a carrier for controlled release of ibuprofen. Ibuprofen was selected as the model drug. One step synthesis was proposed and optimized

for preparation of silica dry composites by using tetraethylorthosilane (TEOS) & 3-aminopropyl triethoxy silane (APTMS) at different molar ratios. The desorption of drug becomes process controlled by the presence of amino propyl groups were explained using various characterizations. All silica carriers studied in this work have been prepared by a one-step synthesis following the sol–gel method. The IR investigation showed the presence of the surface OH groups with its relative peaks. And later on when drug is adsorbed there is a broader peak due to the mutual interaction of hydrogen bond. This low-temperature process offers several advantages: in particular, it assures high homogeneity of the final products. Silica-ibuprofen tablets were functionalized with different amount of aminopropyl groups and evaluated the effect of the organic groups amount on the properties of the obtained carriers (physicochemical properties, stability) and on drug delivery performance.

Jun Lin et al. [71] explained how work on drug delivery was carried out on mesoporous silica which is biocompatible. Implementation of magnetism and luminescence was brought in for various biotechnological and bio medical applications. The ordered mesopores at the shells, on the one hand, can provide accessible channels for drug molecules diffusion and mass transfer without blocking; on the other hand, could control the permeability of the shells for matter exchange between voids and the outer environment. Magnetic nanoparticles, an important category of inorganic material finds its application for targeted drug delivery. The work guides us through how mesoporous silica is used in drug delivery and how functionalization helps followed by the explanation of stimuli-response controlled release systems. Bio-stimuli responsive to deliver desirable molecules involving antibodies, nucleotides need to act as to uncap the mesoporous silica materials at that point.

Siling Wang et al. [72] studied the applicability of chitosan to regulate drug release rate for porous silica for which; coated spherical non silica matrix with chitosan. Carvidiol used as model drug and was loaded using solvent evaporation technique. Charecterization using TEM, XRD, DSC & TGA proved the drug loading. It was inferred that chitosan in acidic

environment showed swelling nature and in the alkaline in is shrinking showing controlled release. The dissolution profiles of the raw drug and drug-loaded composite were studied by using a USP II paddle method with a dissolution apparatus. All dissolution studies were carried out under sink conditions in triplicate. Enzyme free simulated intestinal fluid was used as the medium of release. The chitosan coating process was achieved by a postsynthesis approach. The group also studied the swelling property of chitosan grafted silica.

Yingjug Wang et al. [73] studied the use of hierarchically porous hydroxyapetite microsphere for their role in drug delivery. The work also highlighted the use of citrate which brings with it a dual role of converting the dumb bell shaped hydroxyapatite to individual spheres and importantly a stimuli release mechanism. The reaction was done using one pot synthesis with vancomycin. *In-vitro* of the vancomycin was performed when 0.02g of sample in 20 ml of a media of phosphate buffer, stirring for 12h at room temperature. The group successfully prepared MHAp with a hierarchical porous structure with the thermodynamic treatment to bring with it a controlled release without burst release to make it a promising drug delivery vector. Summarized in their review about the basic idea behind the chemical design classical inorganic porous material: aerogel. The review passes through main heading of sol-gel chemistry, the structure of the gels, and the resulting properties of the light weight aerogel material. In the review, postulate of exchanging the pore liquid which is traditional method showed that it maintains the filigrane solid network. The various drying techniques such as supercritical drying and ambient pressure were elucidated. The versatility with which these aerogels can be used as aerogel films, carbon aerogels and hybrid inorganic-organic aerogels were also reported. The authors conclude that preparation of aerogels is “nanotechnology” which possesses unique optical, thermal, acoustic and mechanical properties. Ambient pressure drying brings new light in to this field as aerogels can be prepared in normal laboratory scale.

Shah et al. [74] reviewed the Pharmaceutical applications of aerogels. The author identified aerogels one of the emerging and most promising means of drug delivery system. In this

review, it was reported that along with the innovative properties such as low thermal conductivity, refractive index, thermal stability, and large surface area biocompatibility of aerogels, make them a potential candidate as a drug carrier.

Smirnova [75] has given a detailed overview of **'Pharmaceutical Applications of Aerogels'** in her book chapter. Biocompatible aerogels and composite aerogel materials in life science, especially in biomedical and pharmaceutical applications were reviewed. Due to their large surface area, open pore structure, and biocompatibility, aerogels are very promising candidates for drug delivery systems. The use of both inorganic and organic aerogels as carriers for pharmaceutically active compounds is discussed in the chapter. Both the stability and the release kinetics of the drug can be significantly improved by loading them into aerogels. First attempts to prepare semisolid and solid pharmaceutical formulations have been mentioned. Furthermore, aerogels applications as host matrix for bioactive compounds (enzymes and proteins) were elucidated. Taking into account all research activities in the area of aerogels, a number of promising pharmaceutical applications can be expected in future. Extensively carried out her work on aerogels as tailor made carriers for drug release. The potential of inorganic polymeric materials of silica was studied. Poorly soluble drugs can be adsorbed on silica aerogels and gets distributed in molecular level. The possibility of producing both hydrophilic and hydrophobic gels was studied. The loading of aerogels with drugs was reported as the maximum possible loading that could be achieved by the application of supercritical CO_2 environment. Several factors come in to play major role. The hydrophilic silica aerogels rapidly collapses in water so drug might be abruptly released. Hydrophobic aerogels have higher density and have comparatively smaller pore size permitting a more controlled release of the drug entrapped within.

Rakesh Patel et al. [76] envisaged the work on silica aerogels seeing their wide potential & applications. The article explains the multi dimensional use of aerogels in various fields such as molecular imprinting, agriculture, as a replacement for aerosil etc. He also explained that aerogels can be used as carriers for drug delivery and addressed the

synthesis, properties and characterization of silica aerogels their field of pharmaceuticals and future prospects. This method can be used as an alternative to the micronization procedure, used for these purposes at present time. Aerogels show great promise for use in variety of technological areas where special structure and physical.

Mohammad Alnaief [77] studied various applications of silica aerogels. Studied were extended to different approaches for production of micro spherical aerogel particles. A combination of sol-gel process with the emulsion process followed by supercritical extraction of the solvent from gel-oil dispersion was studied. Micro spherical alginate aerogel beads with exceptional high surface area were produced. The author used a novel technique for the coating of aerogel materials an experimental spouted bed apparatus was used, the process can be carried out in a batch process. The particle size from the nozzle was measured using laser diffraction spectroscopy. The aerogels coated with Eutragit gave a release of 20 percent lesser than the adsorbed one within 120 minutes, showing its nature as pH sensitive drug release.

M. Alnaief et al. [78] experimented on converting the aerogels which were before proved to have a good surface area and biocompatibility to a substance which could hold more amount of drug. This property was brought about by surface functionalization with an amino group which provided the desired results. The modified aerogels offer more active absorption sites for the drugs. it was possible to produce a transparent amino-functionalized aerogel with a BET surface area of 960 m^2/g, which is more than two times larger than that obtained by other groups. By increasing the number of amino groups on the surface the amount of drug loaded could also be improved. Here it is possible to design a carrier for a particular drug or for controlled release of that drug in the media.

Smirnova et al. [79] reported the feasibility of silica aerogels as oral drug delivery systems. Silica aerogels were loaded with several drugs by adsorption from their solutions in

supercritical CO_2. It was demonstrated that for all three drugs investigated, high loading of the aerogel could be achieved. The loaded aerogels were characterized by IR- and UV spectroscopy and X-ray diffraction in order to show that no degradation of the drugs occurred during the loading procedure. The release profiles of two drugs (ketoprofen and griseofulvin) from loaded aerogels were measured. It was found that the drugs adsorbed on hydrophilic silica aerogels dissolve faster than the corresponding crystalline drugs. This fact can be explained by both an increase in the specific surface area of the drug adsorbed on the aerogel and its non-crystallinity in this state. The influence of density and hydrophobicity of aerogels on both the adsorption and release of drugs were also studied.

Giuseppe Caputo[80] studied supercritical adsorption coupled with the high adsorption capacity of silica aerogel a new kind of delivery systems of poor water soluble drugs. In order to overcome drawbacks of conventional techniques where the use of liquid solvents can cause the fracture of aerogel porous structure, in this work a new adsorption process of drugs from a supercritical mixture is proposed. Adsorption takes place from a fluid solution of the drug in supercritical CO_2 and ethanol as co-solvent. A fixed bed adsorption plant has been developed to allow fast mixing of fluid phase and effective contact in the adsorption column. The use of ethanol as co-solvent allows to overcome the limitation of supercritical adsorption due to low solubility of many drugs in supercritical CO_2. Adsorption isotherms were measured for one-model substance, nimesulide, at 40°C, and breakthrough curve was experimentally obtained. The drug loading of the drug into silica aerogel was up to 9 wt%. The drug composite was characterized using scanning electron microscopy, and release kinetics of the adsorbed drug were also evaluated by in vitro dissolution tests. The dissolution of nimesulide from loaded aerogel is much faster than dissolution of crystalline nimesulide. Around 80% of nimesulide dissolves from the aerogel within 6 minutes, whereas dissolving 80% of the crystalline drug takes about 90 min.

Garcia-Gonzalez et al. [81] reported the use of polysaccharides based aerogels carrier for drug delivery system. The biodegradability and biocompatibility of these biopolymers,

coupled to the large variety of chemical functionalities, make them promising carriers for drug delivery systems. Polysaccharide-based aerogels result in highly porous (90–99% porosities), lightweight (ρ=0.07–0.46g/cm3) drug carriers with high surface area (S =70–680m2/g), able to provide enhanced drug bioavailability and drug loading capacity. This review focuses on the state-of-the-art of the production of polysaccharide-based aerogels with emphasis on the influence of processing parameters on the resulting end material properties. Case studies on polysaccharide-based aerogels from several sources and as well as their behavior regarding drug loading capacity and release are described.

Zeynep Ulker and Can Erkey [82] in their review described the advances in "aerogel science" and the use of these materials in pharmaceutical sciences for drug delivery applications. Because of their high surface areas, high porosities and open pore structures which can be tuned and controlled by manipulation of synthesis conditions, nanostructured aerogels represent a promising class of materials for delivery of various drugs as well as enzymes and proteins. Along with biocompatible inorganic aerogels and biodegradable organic aerogels, more complex systems such as surface functionalized aerogels, composite aerogels and layered aerogels have also been under development and possess huge potential. Emphasis is given to the details of the aerogel synthesis and drug loading methods as well as the influence of synthesis parameters and loading methods on the adsorption and release of the drugs. Owing to their ability to increase the bioavailability of low solubility drugs, to improve both their stability and their release kinetics, there are an increasing number of research articles concerning aerogels in different drug delivery applications. This review presents an up to date overview of the advances in all kinds of aerogel based drug delivery systems which are currently under investigation.

3.1 AIM OF PRESENT WORK

Aspirin currently finds its clinical application as an antiplateletic drug. For this purpose the amount of aspirin needed is continuous. Controlled release is preferred during medication. The present work aims at developing a new drug carrier which is efficient than the presently used.

Aerogels are nanoporous materials with extremely low bulk density and high specific surface area. Usually they are produced following the sol-gel process followed by suitable solvent removal. In the past few years aerogels have drawn an increasingly attention in different scientific and industrial applications. Because of their outstanding properties, they have been shown to be potential drug carrier systems. The aim of this work is to extend their potential in pharmaceutical applications by filling the gaps that hinder their use in some delivery routes. Three different strategies were implemented to achieve this goal: (1) production of microspherical alumino-siloxane aerogel particles; (2) modifying the surface functionality of the aerogel by surface functionalization (3) and finally loading the aspirin drug for controlled release.

Controlling the dosage quantity in the drug carrier as well as obtaining a specific release mechanism of the loaded drug is of crucial importance in pharmaceutical industry. Functionalization of aerogel surface with specific functional groups that modify the adsorption capacity of the loaded drug can be step toward controlling the dosage quantity. Thiol and Amino functionalization was proposed as a model functionalization for modifying the affinity of alumino-siloxane aerogels towards specific drugs. The main aim of the work is to successfully modify aerogel without affecting the release properties of the aerogels.

Multiporous microspheres are known to have a multi channeled walls which allows the drug to entrap into it and get it released, this concept has to be studied.

The drug entrapment and the release profile on the novel alumino-siloxane aerogel microspheres are to be studied and compare the results with the results given in literature. This work further aims to design the formulation as a pH stimuli release; which selectively

releases the drug only at the intestinal pH. This is brought about by the application of an intermediate step of surface functionalization. Here the drug forms a weak bond with the basic funtionalized outer pores and cleaves this bondage and would release in the intestine (basic pH).

3.2 PLAN OF WORK

PREFORMULATION STUDIES

- Determination of suitable composition for formation of spherical microspheres.
- IR studies to show there is no drug excipient irreversible interaction.

FORMULATION DEVELOPMENT

- Alumina Siloxane aerogel microspheres to be produced.
- Calcining the aerogels to remove all the organic groups.
- IR studies to carried out confirm the removal of organic.
- Drug loading capacity of the aerogel micro beads destainer shaker.
- Surface funtionalization to be done; to improve the drug loading capacity.
- Drug loading process to be carried and confirm with UV experiments the amount of drug loaded in the aerogel microspheres.
- Drug release studies to be carried out at both acidic and basic PBS.

EVALUATION STUDIES

- TGA
- FTIR
- PXRD
- Nitrogen Absorption Analysis BET
- SEM studies
- TEM studies
- UV Analysis

4. METHODOLOGY

4.1 Materials

Table 4.1 Materials used

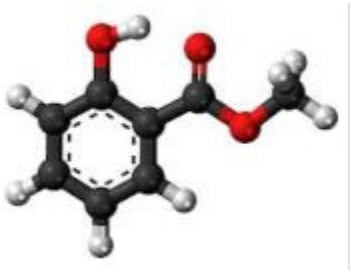
MATERIALS	SOURCE
Aspirin (Acetyl salicylic acid)	Acros Organics, Fisher Scientific, USA
Aluminum Isopropoxide (AIP)	Sigma Aldrich, Purity>98%, USA
Aminopropyl trimethylsilane (APTMS)	Sigma Aldrich, Purity>98%, USA
3- Mercaptopropyl trimethoxysilane (MPTMS)	Sigma Aldrich, Purity>97%, USA
Tetraethylorthosilicate (TEOS)	Sigma Aldrich, Purity>98%, USA
Polyvinyl alcohol(PVA)	S D Fine chem. Ltd. India
Potassium dihydrogen phosphate	S D Fine chem. Ltd. India
Disodium hydrogen phosphate	S D Fine chem. Ltd. India
Isopropanol	Merck, India
Methanol	Merck, India

4.2 Drug Profile[83]

Chemical and physical data

Name : Aspirin

Chemical Structure



Chemical Name : 2-acetyloxybenzoicacid
Acetylsalicylic acid

Molecular formula : $C_9H_8O_4$

Molecular mass : 180.157 g/mol

Category : Anti plateletic effect

Brand names : Aspent Tab, Aspin 100 Enteric-Coated Tab

Description : White coarse powder, pungency of acetic acid

Solubility	: Soluble in alcohol sparingly soluble in water 3mg/mL (20 °C)
Melting Point	: 136 °C
Density	: 1.40 g/cm^3
Storage	: Must be stored in a cool dry place

Clinical Pharmacology

(a) Mechanism of Action: Platelets provide the initial hemostatic plug at sites of vascular injury. Hence they participate in pathological thrombosis, which in turn lead to myocardial infarction. Aspirin acts on eicosanoids(collective name for arachidonate and related poly unsaturated fatty acids). Interference with the synthesis of eicosanoids is the basis for the effects of many therapeutic agents.

In platelets, the major cyclooxygenase product is thromboxane A_2, a labile inducer of platelet aggregation and a potent vasoconstrictor. Aspirin blocks production of thromboxane A_2 by covalently acetylating the serine residue near the active site of cyclooxygenase, the enzyme that produces the cyclic endoperoxide precursor of thromboxane A_2. As platelets do not synthesize new proteins hence the action of aspirin is permanent one.

(b) Administration: Because of the potent and long lasting effect of low doses of aspirin on platelet function, aspirin is used in the treatment or prophylaxis of disease associated with platelet hyperaggregability, such as coronary artery diseases and post operative deep vein thrombisis. Oral administration is preferred

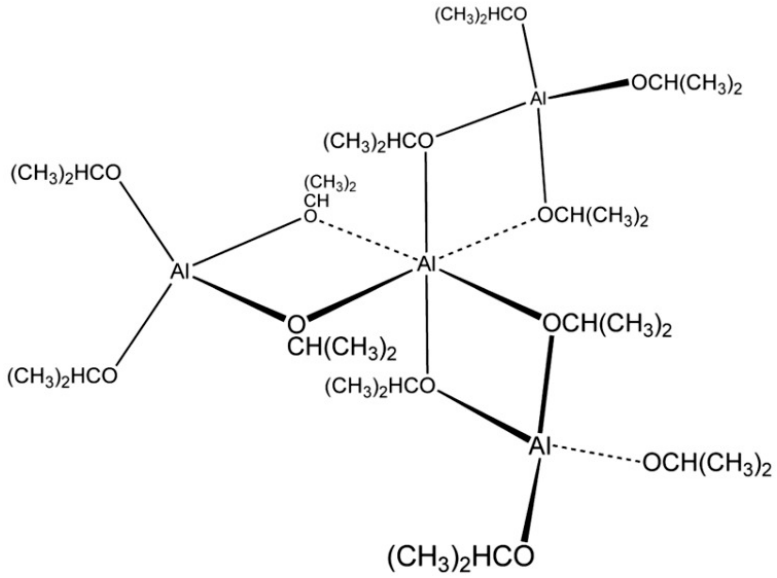
(c) Dosage: The maximum effectiveness of such therapy appears to depend upon selective blockade of TXA_2 synthesis by platelets without preventing production of PGI_2. Selective antiplatelet action appears to be best achieved when the dose of aspirin is 40 to 80mg per day. Higher doses may inhibit PGI_2 production.

4.3. Excipient Profile

4.3a Aluminum Isopropoxide[84]

Molecular Formula : $C_9H_21O_3Al$

Chemical Structure :



Molar Mass : 204.24 g/mol

Appearance : White solid

Density :1.035 g/cm^3, solid

Melting Point : 128-133^{o}C

Solubility : Soluble in water, isoproponol

Description: Aluminium isopropoxide is usually described with the formula Al(O-i-Pr)$_3$, where i-Pr is the isopropyl group ($CH(CH_3)_2$). This colourless solid is useful reagent in synthesis. The structure of this compound is complex, possibly time-dependent, and may depend on solvent.

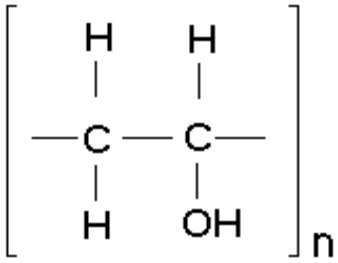
4.3b Polyvinyl Alcohol (PVA)[85]

Synonym : Airvol, Elanol, Polyviol, Poval, PVA,Vinyl alcohol polymer

Chemical Name : Ethenol, Homopolymer

Emperical Formula : $(C_2H_4O)n$

Chemical Structure :



Molecular Weight : 30,000 – 2,00,000

Degree of Polymerization : 1700 - 1800

Description :

Colour : White to cream coloured granular powder

Odour : Odourless

Melting Point : 228°C for fully hydrolyzed grades

Refractive Index : 1.49 – 1.53

Solubility : Soluble in hot or cold water, slightly soluble in some polyhydroxyl compounds, certain amines and amides.

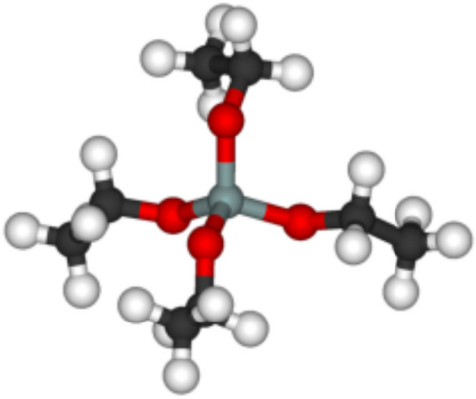
Functional category : Coating agent, Non-ionic surfactant.

4.3c Tetraethyl orthosilicate (TEOS) [86]

Synonym : ethyl silicate, silicic acid tetra ethyl ester

Molecular Fourmula : $SiC_8H_{20}O_4$

Chemical Structure :



Molecular Mass : 208.33 g mol^{-1}

Density : 0.933g/ml at 20°C

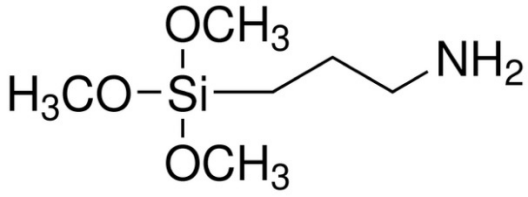
Melting Point : -77 °C

Solubility : Soluble in water but readily decomposes

4.3d (3-Aminopropyl)trimethoxysilane (APTMS)

Synonym : Aminopropyl trimethoxysilane

Chemical Structure :



Boiling Point : 91- 92°C 15 mmHg

Density : 1.027 g/ml at 25 °C

4.4 Instruments

Table 4.2 Instruments used

EQUIPMENTS	COMPANY
Magnetic Stirrer	Remi moters Ltd., Mumbai
Laboratory Oven	Labline instrument, India
Vaccum Oven	Amkette industries
High temperature Furnace	Nabertherm, Germany
pH Meter	Mettler Toledo
UV Spectrophotometer (UV)	Shimadzu, Japan
FTIR Spectrophotometer (FTIR)	Nicolet Magna-560
Powder X-Ray Diffraction (XRD)	X'Pert Pro, Philips
Scanning Electron Microscopy (SEM)	SEM-JEOL 5600 SL
Transmission Electron Microscopy (TEM)	JEOL, 200 CX, TEM
Thermo Gravimetric Analysis (TGA)	Mettler TG 50, Shimadzu, Kyoto
Nitrogen Sorption Measurements (BET)	Micromeritics Gemini 2375
Destainer Shaker	Scigenics Biotech, Orbitek
Optical Microscope	Leica MZ 16 A

4.4.1 Powder X-Ray Diffraction (XRD)

X-ray crystallography is the science of determining the arrangement of atoms within a crystal from the manner in which a beam of X-rays is scattered from the electrons within the crystal. In X-ray crystallographic analysis the pattern produced by the diffraction of X-rays through the closely spaced lattice of atoms in a crystal is recorded and then analyzed to reveal the nature of that lattice. Diffraction effects are observed when electromagnetic radiation impinges on periodic structures with geometrical variations on the length scale of the wavelength of the radiation. The inter atomic distances in crystals and molecules amount to 0.15–0.4 nm which correspond in the electromagnetic spectrum with the wavelength of x-rays having photon energies between 3 and 8 keV. Accordingly, phenomena like constructive and destructive interference should become observable when crystalline and molecular structures are exposed to x-rays. The X-ray diffraction pattern of a pure substance is, therefore, like a fingerprint of the substance. The powder diffraction method is thus ideally suited for characterization and identification of polycrystalline phases. The spacing in the crystal lattice can be determined using Bragg's law. The fundamental equation that gives a relation between the wavelength of X-rays and the spacing in the crystal is the Bragg's equation. Thus, the condition for a diffraction to occur

is: $2d \sin\theta = n\lambda$ where, d is the inter planar distance, λ is the wavelength of X-ray, θ is the angle of diffraction, n is the integer representing the order of the diffraction peak. The diffraction peak is typically a plot of the scattering intensity vs. the scattering angle 2θ. The peak positions, intensities, peak width and peak shape all provide important information about the structure of the material. A sharper peak with high scattering intensity indicates that the sample has good crystallanity. The peaks in an X-ray diffraction pattern are also related to the unit cell dimensions.

4.4.2. Scanning Electron Microscopy (SEM)

A scanning electron microscope (SEM) is a type of electron microscope that images a sample by scanning it with a beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity. These signals include secondary electrons, back scattered electrons, characteristic X-rays and light. SEM is a powerful method for the investigation of surface structures of. This technique provides a large depth of field, which means, the area of the sample that can be viewed in focus at the same time is actually quite large. SEM has also the advantage that the range of magnification is relatively wide allowing the investigator to easily focus in on an area of interest on a specimen that was initially scanned at a lower magnification. The basic steps involved in SEM sample preparation include surface cleaning, stabilizing the sample with a fixative, rinsing, dehydrating, drying, mounting the specimen on a metal holder, and coating the sample with a layer of a material that is electrically conductive.

In a typical SEM, electrons are thermionically emitted from a tungsten filament cathode and are accelerated towards an anode. The electron beam, which typically has an energy ranging from a few hundred eV to 40eV, is focused by one or two condenser lenses into a beam. The beam passes through pairs of scanning coils or pairs of deflector plates in the electron column, typically in the final lens, which deflect the beam horizontally and vertically so that it scans in a raster fashion over a rectangular area of the sample surface. When the primary electron beam interacts with the sample, the electrons lose energy by repeated scattering and absorption within the specimen. The energy exchange between the

electron beam and the sample results in the reflection of high-energy electrons by emission of secondary electrons and the emission of electromagnetic radiation which can be detected to produce an image.

Microstructure analyses of alumina aerogel beads with each of the DCCAs (calcined) were taken. Studs were polished initially with fine graded carbon paper and carbon tape is fixed on it. The beads were mounted on the studs and pasted with a conductive material. In our present study we used Scanning Electron Microscope (SEM-JEOL 5600 SL), for the analyzing the morphology and meso porosity.

4.4.3. Transmission Electron Microscopy (TEM)

Transmission electron microscopy (TEM) is a microscopy technique whereby a beam of electrons is transmitted through an ultra thin specimen, interacting with the specimen as it passes through. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor such as a CCD camera.

In TEM electrons are accelerated to 100 KeV or higher (up to 1MeV), When electrons are accelerated up to high energy levels (few hundred KeV) and focused on a material, they can scatter or backscatter elastically or inelastically, or produce many interactions, source of different signals such as X-rays, Auger electrons or light Figure 4.1. The beam of electrons transmitted through an ultra thin specimen, interacting with the specimen as it passes through. The scattering processes experienced by electrons during their passage through the specimen determine the kind of information obtained. An image is formed from the interaction of the electron transmitted through the specimen are magnified and focused onto an imaging device, such as a fluorescent screen, on a layer of photographic film, or to be detected by a sensor. TEM are capable of imaging at a significantly higher resolution than light microscope, owing to the small de Broglie wavelength of electrons. This enables the instrument's user to examine fine details- even as small as a single column of atoms, which is tens of thousands times smaller than the smallest resolvable object in a light microscope.

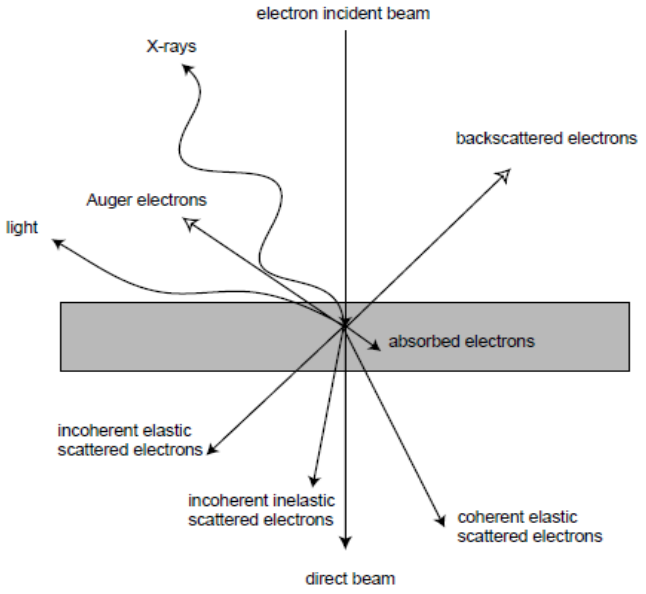


Figure 4.1 Electron scattering in conventional TEM

At smaller magnifications, TEM image contrast is due to absorption of electrons in the material due to the thickness and composition of material. At higher magnifications complex wave interactions modulate the intensity of the image, requiring expert analysis of observed images. Alternate modes of use allow for the TEM to observe modulation in chemical identity, crystal orientation, electronic structure and sample induced electron phase shift as well as the regular absorption based imaging. In the case of a crystalline material, electron diffraction will not only occur at specific angles, which are characteristic for the crystal structure present. As a result, a diffraction pattern of the irradiated area is created that can projected onto the CCD camera. In this way electron diffraction can provide crystallographic information from thin films, bulk material as well as from nanometer sized particles. The greatest advantages that TEM offers are the high magnification ranging from 50 to 10^6 and its ability to provide both image and diffraction information from a single sample. For the present study, Transmission electron microscopy images were recorded using a JEOL, 200 CX, TEM.

4.4.4 Fourier Transform Infrared Spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. This confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time. FTIR has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared), opening up new applications of infrared spectroscopy. Fourier Transform Infrared (FTIR) spectrometry was developed in order to overcome the limitations encountered with dispersive instruments. The main difficulty was the slow scanning process. A method for measuring all of the infrared frequencies simultaneously, rather than individually, was needed. A solution was developed which employed a very simple optical device called an interferometer. The interferometer produces a unique type of signal which has all of the infrared frequencies "encoded" into it. The signal can be measured very quickly, usually on the order of one second or so. Thus, the time element per sample is reduced to a matter of a few seconds rather than several minutes. The development of reliable FTIR instrumentation and strong computerized data-processing capabilities has greatly improved the performance of quantitative IR work. The basis for quantitative analysis of absorption spectrometry is the Bouguer-Beer-Lambert law,

$$A = abc$$

Deviations from Beer's law occur more often in infrared spectroscopy. However, coupling of the advancement of computerized FTIR instrumentation can make FTIR a viable option for reliable quantitative analysis.

FTIR analysis provides information about the chemical bonding or molecular structure of materials, whether organic or inorganic. The technique works on the fact that bonds and groups of bonds vibrate at characteristic frequencies. A molecule that is exposed to infrared rays absorbs infrared energy at frequencies which are characteristic to that molecule. The FTIR spectrum is equivalent to the "fingerprint" of the material. During FTIR analysis, a spot on the specimen is subjected to a modulated IR beam. The resulting FTIR spectral pattern is then analyzed and matched with known signatures of identified materials in the FTIR library.

4.4.5 Thermo Gravimetric Analysis (TGA)

Thermo gravimetric analysis (TGA) is an analytical technique used to determine a material's thermal stability and its fraction of volatile components by monitoring the weight change that occurs as a specimen is heated. It relies on a high degree of precision in three measurements: weight, temperature, and temperature change. As many weight loss curves look similar, the weight loss curve may require transformation before results may be interpreted. A derivative weight loss curve can be used to tell the point at which weight loss is apparent. It is commonly employed to determine degradation temperatures, absorbed moisture content of materials, the level of inorganic and organic components in materials, decomposition points of explosives and solvent residues.

The analyzer usually consists of a high-precision balance with a pan loaded with the sample. The sample is placed in a small electrically heated oven with a thermocouple to accurately measure the temperature. The maximum temperature is selected so that the specimen weight is stable at the end of the experiment, implying that all the chemical reactions are completed (i.e., all of the carbon is burnt off leaving behind metal oxides). The atmosphere may be purged with an inert gas to prevent oxidation or other undesired reactions. Analysis is carried out by raising the temperature gradually and plotting weight against temperature.

4.4.6 Nitrogen Sorption Measurements (BET Surface area analysis)

Surface area and porosity nature was studied by standard N_2 adsorption technique using surface area analyzer, after degassing the samples at 200 °C for 2 h. Nitrogen sorption measurements are the most common methods for the determination of porosity related parameters such as specific surface area or pore radii. Nitrogen is cheap, it is not very reactive and the main interaction with the surface is given by physisorption. For a typical measurement, the sample is evacuated at elevated temperatures to remove adsorbed water. For the measurement the sample is cooled down to the temperature of liquid nitrogen of 77 K. Gaseous nitrogen is then added step by step in small portions. Keeping the system in equilibrium between the adsorbed gas and the free gas, the pressure in the respective volume will change. A plot of the adsorbed volume in dependence of the relative pressure p/po, where p denotes the equilibrium pressure and

po the saturation vapor pressure, gives the so-called adsorption isotherm, which slope strongly depends on the nature of the sample. In Figure 4.2 typical adsorption isotherms are shown:

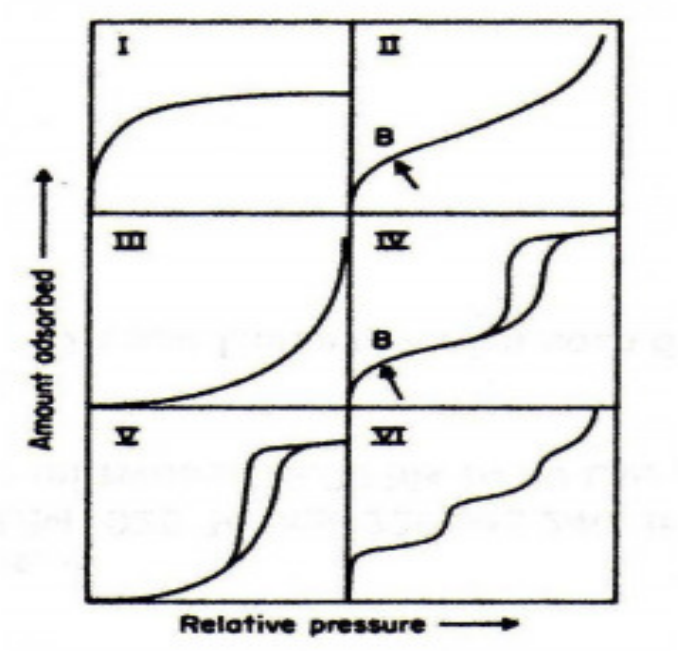


Figure 4.2 IUPAC classification of sorption isotherms

Following the IUPAC classification of sorption data, the Type I thus identifies a microporous material due to the steep increase of the adsorbed volume at low relative pressures. A Type II isotherm is observed for non- or macroporous materials. The point B (marked with an arrow in Figure 4.2) denotes the onset of multilayer adsorption. Type III is obtained for a weak interaction of the gas with the surface. Type V isotherms are very uncommon, but observed for certain systems like graphite, which shows a weak interaction with water molecules together with some porosity. At higher relative pressures, capillary condensation may be observed, which means that inside the pores liquid gas is formed even before the saturation pressure is reached. The capillary condensation strongly depends on the pore diameter and for small diameters condensation is observed earlier. Type VI is observed for layer by layer adsorption on a uniform non-porous surface. Finally, Type IV is the typical isotherm one would observe for a mesostructured material.

4.4.7 Ultraviolet-Visible Spectroscopy (UV)

Absorption of light by solution is one of the oldest and still one of the more useful instrumental methods. The wavelength of light that a compound will absorb is characteristic of its chemical structure. Specific regions of the electromagnetic spectrum are absorbed by exciting specific types of molecular and atomic motion to higher energy levels. Absorption of visible and ultraviolet (UV) radiation is associated with excitation of electrons, in both atoms and molecules, to higher energy states. All molecules will undergo electronic excitation following absorption of light, but for most molecules very high energy radiation (in the vacuum ultraviolet, <200 nm) is required. For molecules containing conjugated electron systems however, light in the UV-visible region is adequate (e.g., benzene absorbs in the 260 nm region). As the degree of conjugation increases, the spectrum shifts to lower energy. Thus naphthalene absorbs light up to 300 nm, and anthracene absorbs to about 400 nm. Because absorption spectra are characteristic of molecular structure, they can be used to qualitatively identify atomic and molecular species.

Ultraviolet–visible spectroscopy and near-infrared or ultraviolet-visible spectrophotometry (UV-Vis or UV/Vis) refers to absorption spectroscopy or reflectance spectroscopy in the ultraviolet-visible spectral region. This means it uses light in the visible and adjacent (near-UV (NIR)) ranges. The absorption or reflectance in the visible range directly affects the perceived color of the chemicals involved. In this region of the electromagneticspectrum, molecules undergo electronic transitions. This technique is complementary to fluorescence spectroscopy, in that fluorescence deals with transitions from the excited state to the ground state, while absorption measures transitions from the ground state to the excited state.

The amount of light, I, transmitted through a solution of an absorbing chemical in a transparent solvent can be related to its concentration by Beers Law:

$$-\log I/I_o = A = \varepsilon_\lambda bc$$

Where I_0 is the incident light intensity, A is the absorbance (a defined quantity, also referred to as the optical density, or OD), b is the cell path length in cm, c is the solution concentration in moles/liter, and ε_λ is the molar absorptivity.

The instrument used in ultraviolet-visible spectroscopy is called a UV/vis spectrophotometer. It measures the intensity of light passing through a sample (I), and

compares it to the intensity of light before it passes through the sample (I_0). The ratio I/I_O is called the transmittance, and is usually expressed as a percentage (%T). The absorbance, A is based on the transmittance:

$$A = -\log (\%T / 100\%)$$

A spectrophotometer can be either single beam or double beam. In a single beam instrument all of the light passes through the sample cell. I_0 must be measured by removing the sample. In a double beam instrument, the light is split into two beams before it reaches the sample. One beam is used as the reference; the other beam passes through the sample. Some double beam instruments have two detectors (photodiodes), and the sample and reference beam measured at the same time. In other instruments the two beams pass through the beam chopper, which blocks one beam at a time. The detector alternates between measuring the sample beam and the reference beam. The resulting spectrum is presented as a graph of absorbance (A) versus wavelength (λ).

5. EXPERIMENTAL INVESTIGATION

5.1 Method of preparation of alumino-siloxane aerogel microspheres

Alumino-siloxane aerogel microspheres were prepared by sol-gel method via ambient pressure drying. The raw material for the synthesis of alumina sol was AIP. AIP was a cheaper alkoxide with similar property that of aluminum tertiary or secondary butoxide. Alumina sol of 1M concentration was prepared by the hydrolysis and condensation reaction of AIP by modified Yoldas process[87] . In this experiment the precursor AIP was first hydrolyzed in water at 80-85 ºC. The initial hydrolysis temperature of 80 °C was chosen because it is the highest temperature compatible with avoiding violent boiling caused by the exothermic hydrolysis and condensation reactions. After hydrolysis and condensation, acid was added to cause peptization and the resultant sol was refluxed overnight for more than 12 hrs at 95-100º C to form a clear, stable, colloidal sol. The reaction is given by the equation

$$Al(O\text{-}C_3H_7)_3\ (l) + (n+2)\ H_2O(l) + HCl\ (aq) \longrightarrow AlO(OH).nH_2O(s) + 3C_3H_7OH(g)$$

To the hydrolyzed alumina sol containing 4g Al_2O_3, weighed amount of PVA was added and stirred for 30 min. Subsequently, weighed amount of 3-Aminopropyl trimethoxysilane was added drop wise. The resultant alumina/silanes stiff gel was again peptized by adding nitric acid up by adjusting the pH to 3 and stirred for 1h to obtain sol - gel mixture of alumino-siloxane.

The partially gelled sol was then sprayed through the syringe. The sol droplet passes through an oil layer as shown in experimental set in Figure 5.1. Various compositions selected for the experiment are given in Table 5.1. Spherical wet gel microspheres were formed due to surface tension. The wet gel microspheres then fell into an ammonia solution placed right underneath the oil. After aging in ammonia solution for about 1 hr, the microspheres are then withdrawn from ammonia solution, carefully sieved and washed with water and alcohol to eliminate oil and ammonia residues. The microspheres were then washed with isopropanol several times within 24 hours so as to remove water from pores. During washing process the beads were kept at 50º C, this was followed by aging the samples in TEOS solution for 48 hours at 50º C and the final solvent exchange with isopropanol. The microspheres were then dried in tightly closed containers at 50º C.

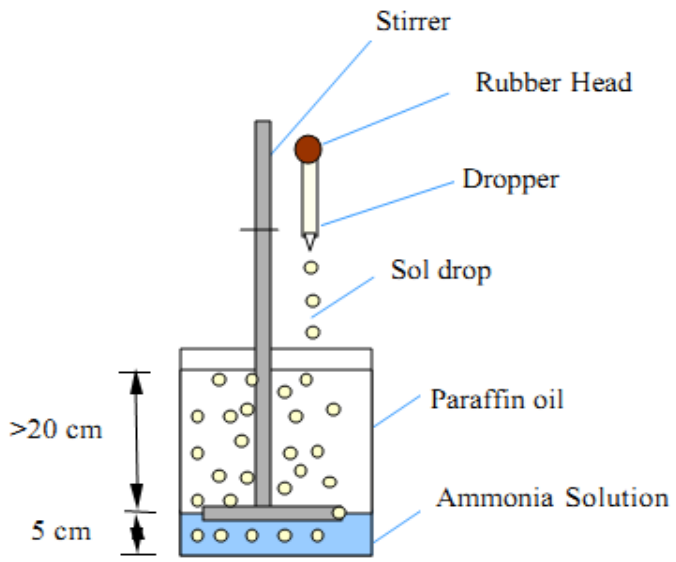


Fig 5.1 Schematic representation of alumino- siloxane microspheres formation

Table 5.1 Composition of samples prepared

Sample code	H_2O/AIP (molar ratio)	APTMS/AIP (molar ratio)	PVA (wt %)	Viscosity of the gel (Pa.s)	Shape	Shrinkage (%)
A1	60	0.38	5.0	7.81	Irregular	13
A2	70	0.38	5.0	3.41	spherical	15
A3	80	0.38	5.0	2.14	spherical	18
A4	90	0.38	5.0	1.40	spherical	25
A5	100	0.38	5.0	1.23	spherical	36
A6	80	0.38	0.0	2.45	Cracked	----
A7	80	0.38	2.0	2.75	spherical	14
A8	80	0.38	3.0	2.40	spherical	15
A9	80	0.38	5.0	2.54	spherical	15
A10	80	0.38	8.0	2.98	Cracked	-----
A11	**80**	**0.09**	**5.0**	**2.56**	**spherical**	**13**
A12	**80**	**0.19**	**5.0**	**2.74**	**spherical**	**14**
A13	**80**	**0.38**	**5.0**	**2.43**	**spherical**	**16**
A14	**80**	**0.56**	**5.0**	**2.12**	**spherical**	**16**
A15	**80**	**0.75**	**5.0**	**2.45**	**spherical**	**15**
A16	80	0.95	5.0	3.00	Cracked	----

The best formulated selected out of the above formulation was subjected to further studies based on the shrinkage, shape and density of the samples. The above samples were further calcined to remove the organic template at 600 °C. Samples A11, A12, A13, A14 and A15 calcined at 600 °C are denoted as $A11^1$, $A12^1$, $A13^1$, $A14^1$ and $A15^1$ respectively. The samples $A11^1$, $A12^1$, $A13^1$, $A14^1$ and $A15^1$ were selected for further studies, for drug

loading. $A15^1$ sample found to have maximum drug loading capacity. (Detailed explanation is given in chapter 6). From the literature it is clear that functionalization can improve loading of drug. To prepare functionalized aerogel microspheres by post-synthesis, maximum drug loaded sample ($A15^1$) were selected and following procedure adopted for loading.

5.2 Surface functionalization of aerogel microspheres with organotrialkoxy silane (APTMS and MPTMS)

Prior to surface modification, aerogel microspheres (A15) dried at 110° C in a vacuum oven for 15 h to remove moisture adsorbed at the surface. 0.3g of samples was then dispersed in dry toluene. 1, 2, 3 ml of silane (APTMS /MPTMS) was added to the mixture and was refluxed for 20 h under argon atmosphere. Dry toluene was used in order to prevent homo polycondensation of silane. This also promotes local hydrolysis of silane methoxy (Si–O–Me) groups to Si–OH, which then undergo condensation with –OH groups at the closest proximity of the surface and pores of microspheres. The samples were then washed several times with toluene to remove the unreacted siloxane moieties. The samples were dried under vacuum at 110 °C for 3 h to remove residual toluene.

5.3 Loading of aspirin drug

To load aerogel microspheres with aspirin, 50 mg of the aerogel samples was added to 20 mL of aspirin in methanol solution (2 mg/mL) and soaked for 3 days under stirring until the concentration of the solution did not significantly change; this was done by monitoring the aspirin concentration using a Shimadzu UV spectrophotometer at a wavelength of 296 nm. The amount of drug loaded onto the samples was determined according to the change of concentration before and after soaking. The samples were quickly and thoroughly washed with methanol and dried under vacuum.

5.4 Preparation of Phosphate buffered saline (PBS)

For pH -7.4 [88]

Add 250.0 ml of 0.2 M potassium dihydrogen phosphate R to 393.4 ml of 0.1 M sodium hydroxide.

For pH -2 [88]

Dissolve 8.95 g of disodium hydrogen phosphate R and 3.40 g of potassium dihydrogen phosphate R in water R and dilute to 1000.0 ml with the same solvent. If necessary adjust the pH (2.2.3) with phosphoric acid R.

For pH- 9 [88]

Dissolve 1.74 g of potassium dihydrogen phosphate R in 80 ml of water R, adjust the pH (2.2.3) with 1 M potassium hydroxide and dilute to 100.0 ml with water R.

5.5 In Vitro Drug Release Studies.

The release profiles of model drugs were determined by soaking 50mg of drug loaded sample in 20 mL of PBS (pH 2, 7.4, 9.) under shaking 150 rpm, at room temperature. Predetermined time, replaced by fresh medium, and spectrophotometrically analyzed at wavelength 296 nm.

5.6 Material Characterization Techniques

The following characterization techniques provide information on the effects of the synthesis process on the aerogel, along with the surface and bulk properties of the row and functionalized aerogels microspheres.

(a) Viscosity measurements

The rheological measurements of the alumino-siloxane gels were examined in cylinder and bob method using a stress controlled Anton Paar Rheo Viscometer by the cyclic application and release of shear force. The measurements started 1 h after the gels had formed.

(b) Thermo Gravimetric Analysis (TGA)

During thermal analysis, material samples gain or lose weight due to thermal events, such as decomposition, oxidation or reactions taking place at particular temperatures. Thermogravimetric analysis (TGA) is the thermal analysis of a sample whereby the mass of the sample is measured as a function of temperature and time under controlled temperature in a chosen environment (e.g. air, nitrogen). TGA is used to obtain

characteristic qualitative (composition) as well as quantitative (amount) information of a sample from a thermogram. Thermograms show stable regions and locations of weight changes which are usually specific to various components of the sample undergoing thermal events. The size of the weight change can be used to obtain quantitative analysis of the thermal event such as organic content of a sample.

Thermogravimetric analyses (Mettler TG 50 (Shimadzu, Kyoto) in air) were carried out to detect the decomposition temperature of the organic moieties grafted on the porous aerogel microspheres. Samples were heated from room temperature to 1000 ºC at the heating rate of 10 ºC /min.

(c) Fourier Transform Infrared Spectroscopy (FTIR)

FTIR instruments use an interferometer to obtain an interferogram (i.e. interference pattern obtained from reflected beams), which is then passed through the sample; information at every wavelength is read by the detector during rapid scanning of the interferometer. FTIR is used to obtain absorption spectra of a compound which show unique reflections of the molecular structure of that compound. This information can be used to identify unknown samples, to analyze sample for composition and also to quantify sample components.

The FT-IR spectroscopic measurements row and functionalized materials were carried out using IR Prestige-21 Shimadzu spectrophotometer. The spectra were recorded as KBr pellets of the samples in the wave number range 400-4000 cm^{-1} with a resolution of 4 cm^{-1} in transmittance mode.

(d) Powder X-Ray Diffraction (PXRD)

Powder X-ray diffraction occurs when X-rays and electrons of atoms interact. When the x-rays hit the electrons some are scattered (diffracted). Depending on the arrangement of atoms in a sample, interference of two diffracted rays can be constructive (i.e., their path difference equals an integral number of the incident wavelength) (detailed explanation given in chapter 4; section 4.4.1.)

In this work X'Pert Pro, Philips powder X-ray diffraction system with Cu-Kα radiation (λ=1.54056^o A) was used. The X-ray scans are performed between 2θ values 10^o and 70^o for the phase identification.

(e) Nitrogen Adsorption Analysis

The physical adsorption (physisorption) of gases on porous aerogel surfaces is useful in the characterization of porous nature of solid[89]. A gas (e.g. nitrogen) adsorption isotherm, a plot of relative pressure against volume of gas adsorbed, is used to estimate the type of pores in the solid material, the size of the pores, the total surface area of the solid material and the pore volume. (detailed explanation given in chapter 4; section 4.4.6.)

N_2 adsorption-desorption analysis was done using ASAP 2010C (Micromeritics, USA) system, at liquid N2 temperature (77K) degassing at appropriate temperature for sufficient time to clean the surface of the adsorbents via a multipoint BET method using the adsorption data in the relative pressure (P/P_0) range of 0.09-0.10.. The Brunauer Emmett Teller (BET) method was utilized to calculate the specific surface areas. All the samples were degassed at 200 °C for 2 h prior to BET measurements. Desorption isotherm was used to determine the pore-size distribution using the Barret-Joyner-Halender (BJH) method, assuming a cylindrical pore model.

(f) Scanning Electron Microscope

The scanning electron microscope (SEM) uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimens. The signals that derive from electron-sample interactions reveal information about the sample including external morphology (texture), chemical composition, and crystalline structure and orientation of materials making up the sample. In most applications, data are collected over a selected area of the surface of the sample, and a 2-dimensional image is generated that displays spatial variations in these properties. Areas ranging from approximately 1 cm to 5 microns in width can be imaged in a scanning mode using conventional SEM techniques (magnification ranging from 20X to approximately 30,000X, spatial resolution of 50 to 100 nm).

The surface morphology of composites was observed by using ZEISS EVO 18 Special Edition Scanning Electron Microscope (SEM), operated at 20 kV. Pinch of samples were added to test tube with appropriate solvent, and sonicated, until uniform dispersed solution was obtained. One layer of this solution poured in to the aluminum stub and dried at overnight. This sample was used for the analysis of SEM.

(g) Transmission Electron Microscopy (TEM)

Transmission electron microscope (TEM) is used to greatly magnify specimens using a beam of electrons. The resolution of 100-keV electron is on the order of an atomic size (~ 0.3 nm) as compared to that of a light microscope (~300 nm)[90]. The light microscope can only magnify images about 1000 times but images on an electron microscope can be highly magnified to see atomic details in the sample. This is because the resolving power (minimum distance between two distinct objects) is directly proportional to the wavelength of illumination. The wavelength of electrons at 60 kV is about 5×10^{-3} nm compared to that of visible light (400–800 nm)[91] . Images in TEM are magnified by electromagnetic lenses which control the electrons that pass through the sample to generate extremely fine structural detail of the sample. Based on the thickness of the sample, some of the electrons are scattered. However, at the bottom of the microscope column electrons that pass through the electron transparent sections of the sample are focused on a viewing screen. A range of signals are detected in transmission electron microscopes to obtain images, diffraction patterns, chemical information and other kinds of spectra.

Interior morphological structure of samples were evaluated by transmission electron-microscope was done by recorded using FEI Tecnai 30G^{2}S- TWIN Transmission electron microscope (TEM) operated at an accelerating voltage of 300kV. Pinch of samples were added to test tube with appropriate solvent, and sonicated until uniform dispersed solution was obtained. One drop of this solution poured in to the glossy carbon grid and dried at overnight. This sample was used for the analysis of TEM.

(h) Ultraviolet-Visible Spectroscopy (UV)

Concentration of aspirin in the solution before and after equilibrium was analyzed by UV–visible spectroscopy at λ_{max} = 296 nm, equipped with a quartz cell having a path length of 1cm.

The concentration of drug solution was monitored by UV/Vis spectrophotometer (Shimadzu UV 240 IPC). While the measurements wavelength interval was adjust between 200 and 500 nm and absorption peaks for aspirin were detected in 296 nm.

6. RESULTS AND DISCUSSION

The various results obtained in the project work are presented in this chapter. The results of thermal stability, phase purity, chemical bonding, surface and pore features, and morphology of the prepared aerogels have been presented. The drug loading and release studies are discussed.

6.1 Textural and Structural Analysis of Aerogel Microspheres

6.1.1 Thermal analysis

The shapes of the TGA curves obtained by the heat treatment in oxygen atmosphere of five set of samples A11, A12, A13, A14 and A15 are displayed, Figure 6.1, as a whole resemble closely with each other. The main changes during thermal analysis of the samples correspond to the removal of the organic matrix. As revealed from the TGA, alumino-siloxane aerogels degrades mainly by a three-stage process, and it is destroyed completely at 600 °C. Because the alumina-based material is readily bibulous, some dehydration of gel (100-150 °C) is still visible in the TGA curves.

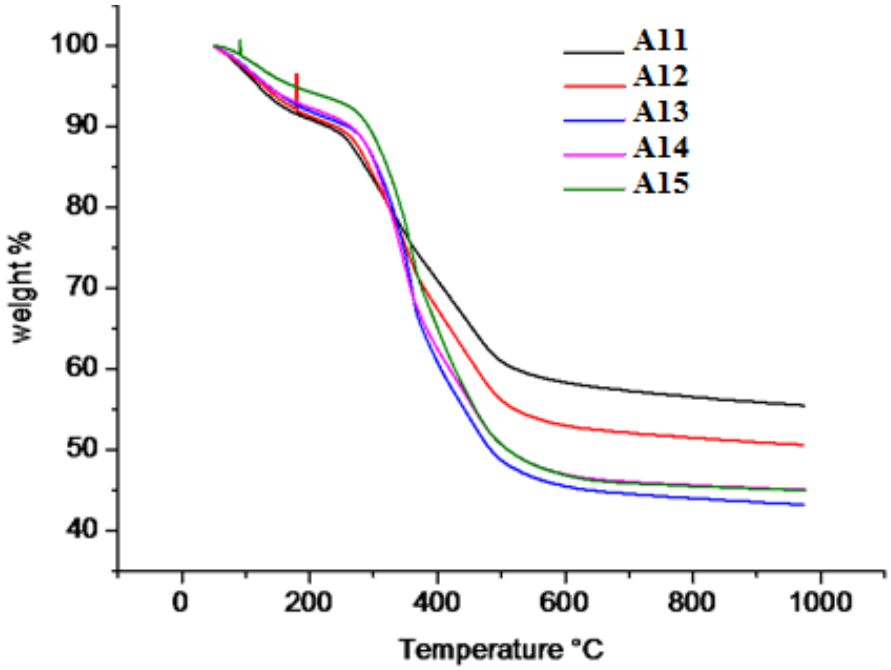


Figure 6.1. TGA curves of the aerogel samples under oxygen at a heating rate of 10 ◦C/min.

The second weight loss occurs for 250-300 °C with a weight loss of 5%, due to the degradation of organic attached in inorganic, and probably due to the release of large amount of organic oxygenated groups formed as a result of the hydrolysis process undergone by the alkoxides which can remain in the organic matrix, either merely trapped inside or even linked to it. The third happens at 460-600 °C with a weight loss of 35%, due to the decomposition of complete organic structures leaving alumino-siloxane Al-O-Si network in the aerogel structure. Complete organic removal with phase stable Al-O-Si network obtained after 600 °C.

6.1.2 Phase analysis

Phase transformation of the as prepared aerogel microsphere and heat treated microspheres at 600 °C was investigated and the results are shown in Figure 6.2 Sample without heat treatment/calcination have a well developed boehmite structure with an amorphous nature of silica and carbon in the skeleton. On heat treatment at 600° C boehmite is converted to -Al_2O_3. The peak at 20-30 range showed a broadening and amorphous nature due to the presence of alumino-siloxane skeleton in the aerogel network.

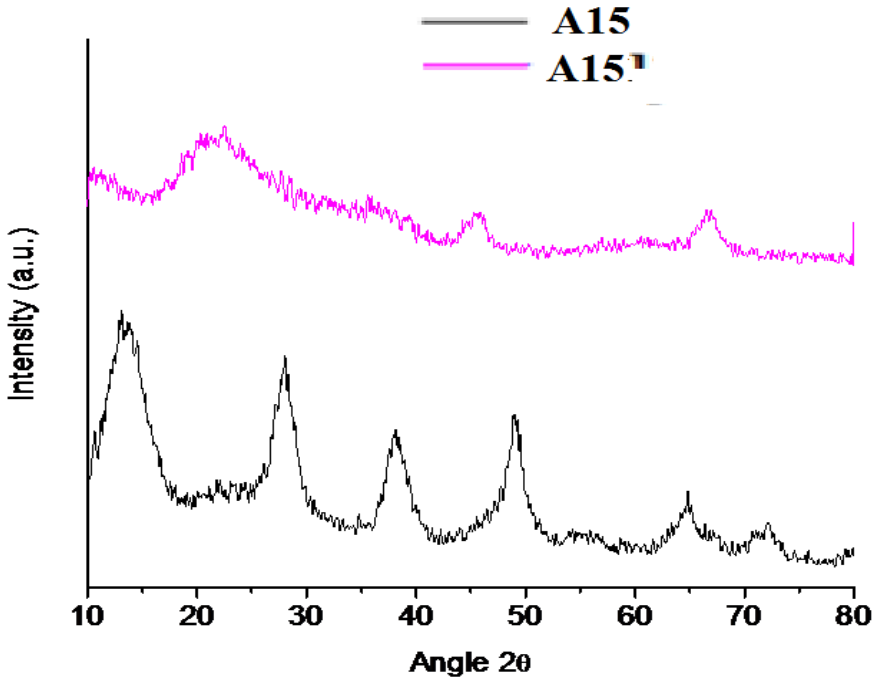


Figure 6.2 X-ray diffraction (XRD) patterns of A15 and A15[1] samples.

6.1.3 Structural analysis

Figure 6.3 shows FTIR spectra of A15[1] and A15, with and without heat treatment/calcination. The FTIR spectrum clearly shows the respective band positions for Al-O and Si-O bonds in the system. In general Al-O and Si-O related vibrations mostly appear in the wavelength region 1200-400 cm^{-1}. For A15 sample the peaks at 3310 cm^{-1}, 1620 cm^{-1}, and 1078 cm^{-1} were assigned to stretching, bending mode of adsorbed water and deformation mode of –OH group, respectively. The deformation mode of free amino group can be found at 1514 cm^{-1}. The vibration bands at 2937 cm^{-1} is attributed to C-H symmetric vibration. Again in A15 bands at 3094 cm^{-1} and 3303 cm^{-1} is assigned to the stretching vibration of N-H from APTMS. This is shows the presence amine functionalityA15. The broadened peak at 1020 cm^{-1} in A15[1] is due to the overlap of Al-O-Si, and Si-O-Si bonding in sol gel reaction, which appears at 1000-1200 cm^{-1} range. A15[1] shows only the major peaks Al-O-Si, and Si-O-Si bonding in its structure, all the peaks due to amine and organic functionality are eliminated after heat treatment at 600°C. All the major peaks are shown in Table 6.1.

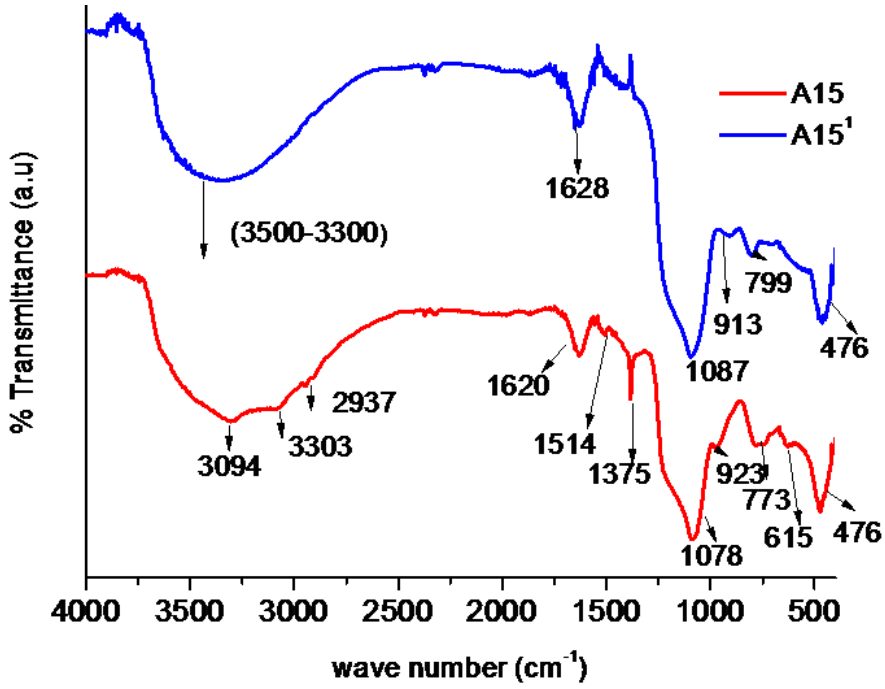


Figure 6.3 FTIR spectra of A15 and A15[1] alumino- siloxane aerogels.

Table 6.1 Bands assigned to various functional groups in FTIR spectra of A15 and A15[1]

Group assigned to A15	Bands (cm^{-1}) assigned to A15	Group assigned to A15[1]	Bands (cm^{-1}) assigned to A15[1]
Si-O-Si stretching	1078	Si-O-Si stretching	1087
Si-O-Si bending	773	Si-O-Si bending	799
Si-O bending	476	Si-O bending	479
Al-O-Si	923	Al-O-Si	913
C-H symmetric	2927	-OH	~3500-3300
N-H stretching	3094,3303	-OH of Al-OH	1628
-OH	~3500-3300		
-OH of Al-OH	1620		

6.1.4 Morphology and microstructure analysis

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) was employed to further understand the microstructure of the alumino-siloxane aerogels and are shown in Figure 6.4 Both SEM Figure 6.4 (b) and TEM Figure 6.4 (c) of the alumino-siloxane aerogels after heat treatment, exhibited typical porous network structures. The framework of aerogels, achieved after the thermal treatment, was uniform and interconnected. The TEM image (c) showed that heat treated aerogels at 600°C exhibited randomly interconnected networks made up of nanometer-sized fibrous γ-Al_2O_3. Figure 6.4 (a) photograph of alumino-siloxane are shown.

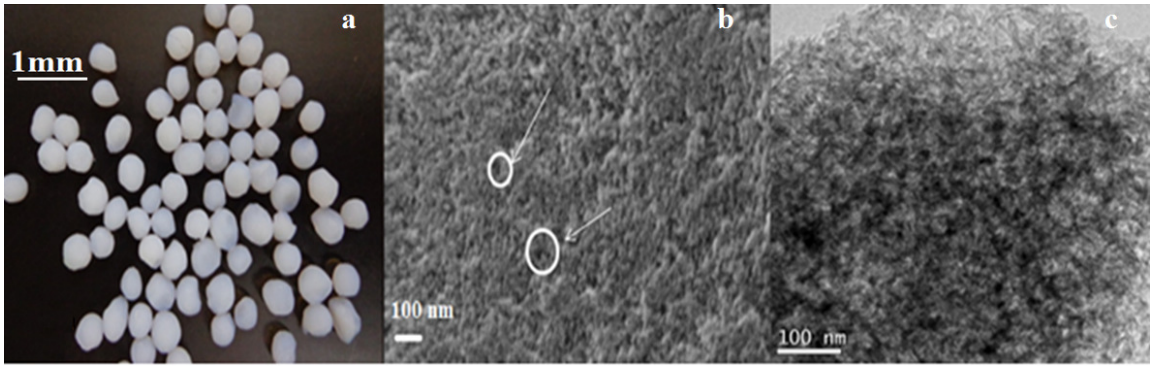


Figure 6.4 (a) Photograph (c) SEM (d) TEM of alumino-siloxane aerogel microspheres (A15[1])

6.1.5 Textural properties

N_2 adsorption–desorption isotherms were performed to further explain the porous structure of aerogel microspheres. As shown in Figure 6.5, isotherms are identified as resembles a type IV and type II curve, according to the IUPAC classification, with a sharp upturn in the high relative pressure, which indicates liquid condensation associated with the presence of large mesopores and macropores. The hysteresis loop of the aerogel samples falls within the H3 and H4 categories, which is typical of slit-type pores generated from the interparticle porosity of fiber-like morphology. Figure 6.6 shows the pore size distribution of alumino-siloxane aerogel microspheres. The pore size was calculated from the desorption branch of the nitrogen isotherm with a BJH model. Pore parameters $A11^1$, $A12^1$, $A13^1$, $A14^1$ and $A15^1$ samples at 600 °C are listed in Table 6.2. The BET surface areas and average diameter of pores decreased from 347 to 261m^2/g and 9.7 to 5.0 nm respectively.

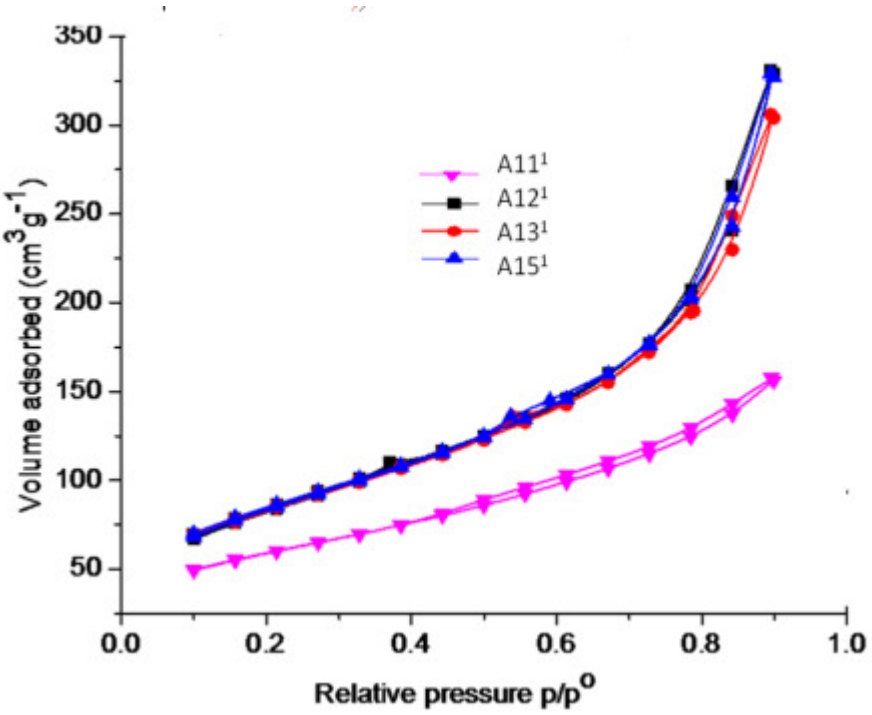


Figure 6.5 N_2 adsorption–desorption isotherms of alumino-siloxane aerogel

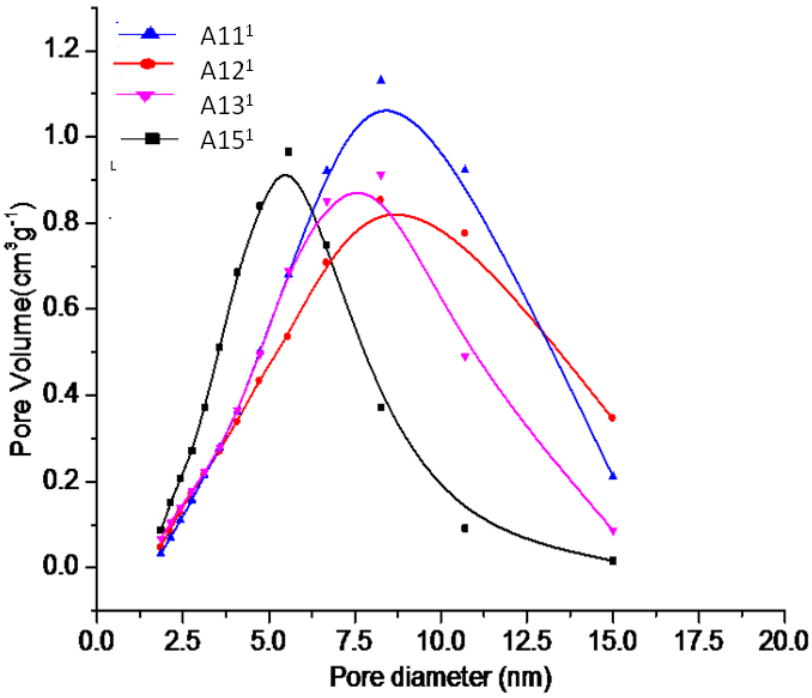


Figure 6.6 Pore size distribution curves of different thermal treated aerogel microspheres.

Table 6.2 Physical characteristics of alumino-siloxane aerogel microspheres

Samples	BET /Langmuir surface area (m^2/g)	Total pore volume (cm^3/g)	Pore diameter (nm)
$A11^1$	347/561	0.4952	9.7
$A12^1$	321/521	0.4312	7.5
$A13^1$	280/449	0.3654	6.7
$A14^1$	234/477	0.3214	5.6
$A15^1$	261/418	0.3124	5.0

6.2 Aspirin Loading and Release

6.2.1 Standard Curve for Aspirin API

Table 6.3 Absorbance measured for preparation of standard curve

Concentration	mg of aspirin
0.04	0.08
0.08	0.16
0.12	0.24
0.16	0.32
0.20	0.40

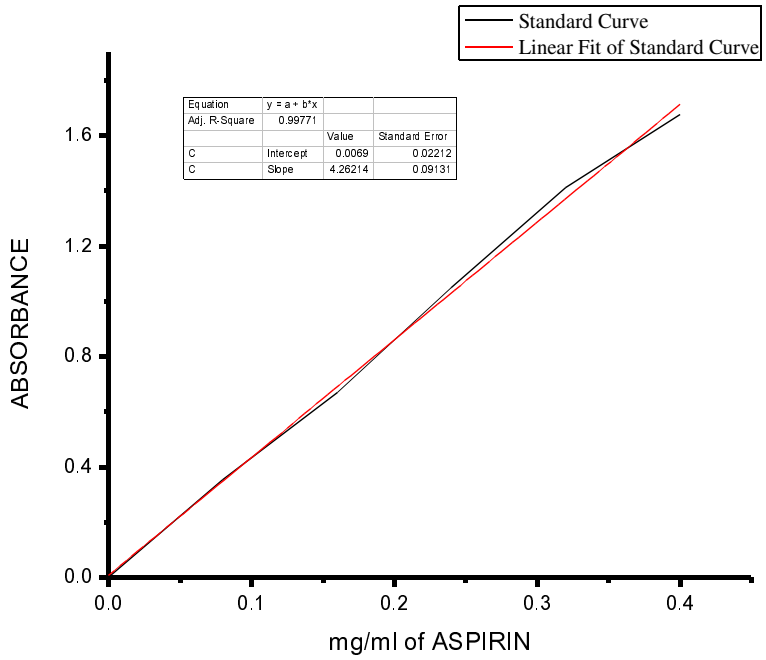


Figure 6.7 Standard curve for aspirin by UV spectroscopy method

6.2.2 Loading aerogel microspheres with aspirin.

Table 6.4 Loading amount of aspirin on different aerogel microspheres.

Sample code	Amount of Aspirin loaded to 50 mg microspheres (mg)	% Loading
Stock solution	-	-
$A11^1$	4.8	12
$A12^1$	5.4	13.5
$A13^1$	9	22.5
$A14^1$	9.8	24.5
$A15^1$	**11.6**	**29**

All samples of aerogel microspheres were soaked in solutions containing drug molecules to entrap drug molecules in "nanoreservoirs", i.e. the nanoporous channels comprising meso and macropores. Table 6.4 displays the adsorption capacities of the aspirin in aerogel microspheres. The result shows that alumino-siloxane aerogel samples with smaller pore-diameter showed high loading of aspirin. Thus formulation suitable for aspirin loading was $A15^1$. This result indicates that pore features play an important role in influencing the adsorption amount of drugs on the surface.

6.2.2 Functionalization of alumino-siloxane aerogel

Since the active drug substances have different functional group, it is possible to enhance their loading as well as the release rate by implementing special functional groups on the surface of the drug carrier by means of functionalization. Hence, we have chosen thiol (-SH) and amine ($-NH_2$) bearing organofunctional silane for surface modification. The aerogel microsphere $A15^1$ loaded maximum amount of drug was selected for surface functionalization. Amine and thiol functionalized samples denoted as $A15^1$ -1NH, $A15^1$ -2NH, $A15^1$ -3NH and $A15^1$ -1SH, $A15^1$ -2SH, and $A15^1$ -3SH, respectively depending on the amount of APTMS and MPTMS used for post grafing.

6.2.3 Characterization of functionalized aerogel microspheres

SEM images of pure aerogel samples, amine and thiol functionalized samples are given in Figure. 6.8. According to SEM images, it is clear that all samples maintained their ordered and stable structure after functionalization process.

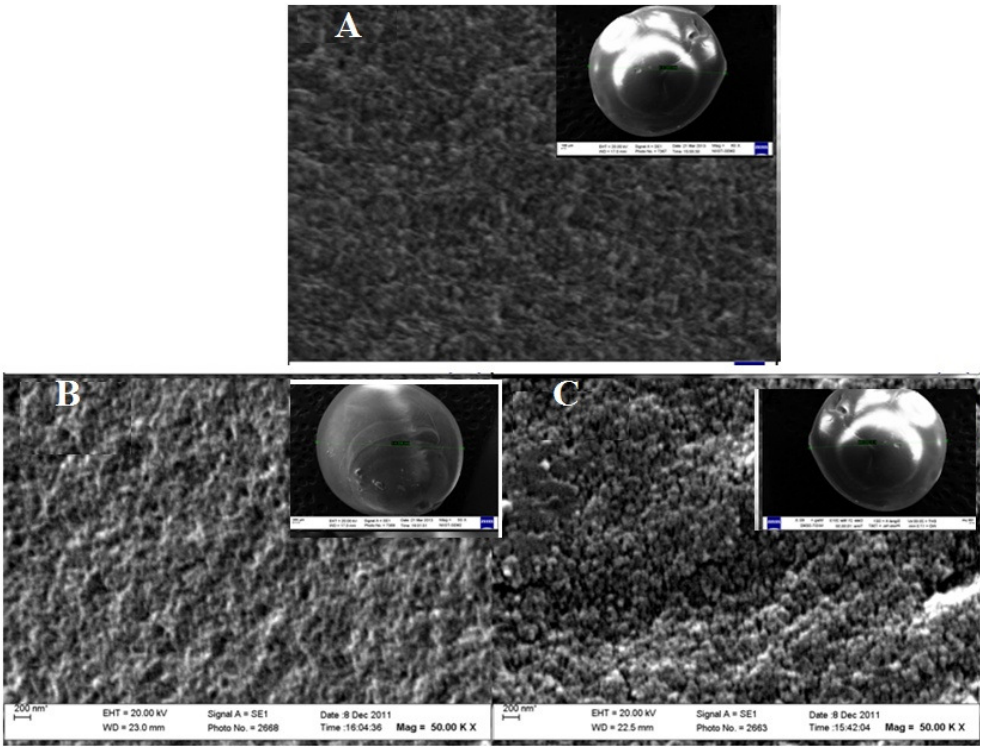


Figure 6.8 SEM of the alumino-siloxane aerogel microspheres (a) A15[1], (b) A 15[1]-2NH, and (c) A 15[1]-2SH

Table 6.5 also lists the N_2 adsorption/desorption data comprising BET and Langmuir surface area, pore volume and pore diameter of functionalized aerogel microspheres prepared by post synthesis (A 15[1]-1NH, A 15[1]-2NH, A 15[1]-3NH, A 15[1]-1SH, A 15[1]-2SH, and A 15[1]-1SH) together with the pure aerogel microspheres (A15[1]), and Figure 6.9 shows their isotherms. The pore size of functionalized aerogels is around 4-2nm, which is smaller than that of A15[1], which has a pore size around 5.0nm. As expected, the introduction of the organic moieties leads to a decrease in pore diameter, surface area and pore volume, and this decrease is more noticeable for the matrix that contains the highest amount of organic material. Furthermore, the marked reduction in pore size shows that the pore wall is indeed decorated by organic moieties. The loss of surface area may be largely attributed to the disappearance of these complementary smaller pores. The isotherms of those prepared by post-synthesis show a very sharp increasing step with a typical H1

hysteresis loop Figure 6.9 corresponding to the highly ordered mesos/macrostructures and narrow pore size distribution.

Table 6.5 Physical characteristic of pure and functionalized aerogels alumino-siloxane aerogel microspheres

Samples	**BET /Langmuir surface area (m^2/g)**	**Total pore volume (cm^3/g)**	**Pore diameter (nm)**
$A15^1$	261/418	0.3124	5.0
$A\ 15^1$-1NH	213/394	0.2154	4.8
$A\ 15^1$-2NH	201/346	0.1450	3.5
$A\ 15^1$-3NH	184/294	0.0996	2.1
$A15^1$-1SH	236/404	0.2365	4.6
$A15^1$-2 SH	198/356	0.1235	3.4
$A15^1$-3SH	189/311	0.1023	2.0
MCM-41	985/1156	0.3254	2.8

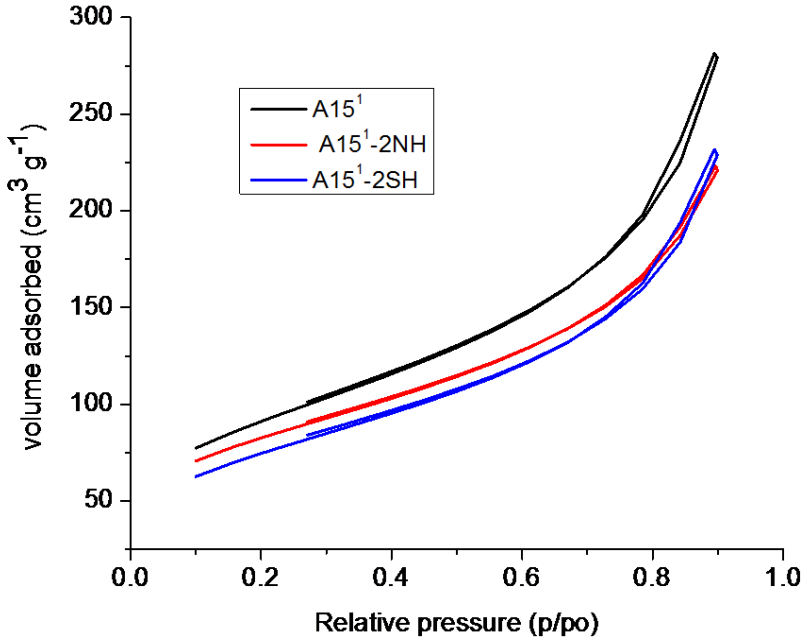


Figure 6.9 N_2 adsorption–desorption isotherms of pure and functionalized alumino-siloxane aerogel

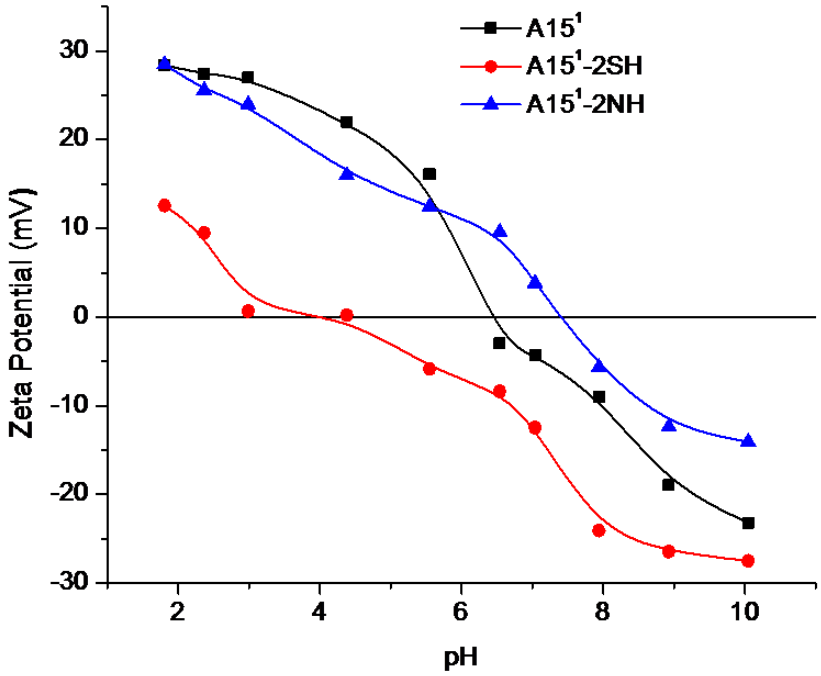


Figure 6.10. Zeta potential of pure ($A15^1$) and functionalized ($A15^1$-2NH, $A15^1$-2SH) alumino-siloxane aerogel at different pH.

We measured the zeta-potential of ($A15^1$) and functionalized ($A15^1$-2NH, $A15^1$-2SH) alumino-siloxane aerogel at different pH in solutions with the pH ranging from 2 to 10 by automatic titration (Figure 6.10). The pH value of point of zero charge (PZC) for $A15^1$, $A15^1$-2NH, and $A15^1$-2SH are 6.8, 7.9 and 4.8 respectively. The zeta potential of $A15^1$-2SH microspheres shifted to negative region for wide range of pH, despite the acidic nature of –SH groups form a negatively charged conjugate base on the surface aerogel microspheres. In microspheres modified with APTMS, the zeta potentials shifted to more positive values due to the presence of protonated amines ($–NH^{+3}$). As a result, isoelectric points of pH 6.8 shifted to pH 7.9 and pH 4.8 for, $A15^1$-2NH, and $A15^1$-2SH modified aerogel samples respectively, in agreement with literature reports[94] .

Loading functionalized aerogel microspheres with aspirin.

To evaluate the capability of the functionalized aerogel microspheres for drug delivery system, aspirin, a typical anti inflammatory drug, was introduced into functionalized samples. The drug loading capacity of the aerogel samples were evaluated and results are described in Table 6.6. For comparison ordered porous MCM-41 was also used.

Table 6.6 Loading amount of aspirin on different aerogel microspheres.

Sample code	Concentration of drug (mg/ml)	Amount of Aspirin loaded to 50 mg microspheres (mg)	Amount of Aspirin loaded to 90 mg microspheres (mg)	% Loading
Stock solution	-	-	-	-
$A11^1$	0.176	4.8	8.64	12
$A12^1$	0.173	5.4	9.72	13.5
$A13^1$	0.155	9	16.20	22.5
$A14^1$	0.151	9.8	17.64	24.5
$A15^1$	0.142	11.6	20.88	29
A 15^1-1NH	0.132	13.5	24.30	34
A 15^1-2NH	0.110	18	40.5	45
A 15^1-3NH	0.118	16.4	36.9	41
$A15^1$-1SH	0.089	22.2	39.96	55.5
$A15^1$-2SH	**0.073**	**25.4**	**50.2**	**63.5**
$A15^1$-3SH	0.092	21.6	38.8	54
MCM-41	0.142	10.4	18.72	27.5

From the drug loading analysis it is very clear that after functionalization, the loading ability of aerogel microspheres is enhanced. Maximum drug loading is for samples A15[1]-2NH and A15[1]-2SH. The following formulations were finalized by deriving the drug loaded results.

A 15[1]-2NH, A15[1]-2 SH and MCM-41

The drug loading of a maximum of 50 mg of aspirin was seen in A15[1]-2 SH functionalized aerogel microsphere with a value of 50.2 mg which was loaded into 90mg microspheres. The top three drug loaded aerogel samples were selected for the drug release profile studies. Along with it MCM-41 which is regarded as ordered porous material was also selected for comparative *in-vitro* release study.

The formulations with the drug loading less than 50 mg which is the minimum dosage required were selected so as to study the release profile and if found favorable can be utilized with a higher capsule size with more amount of microsphere.

From this the formulation A15[1]-2 SH was selected and the capsule shells of size 1 were used for filling the aerogel microspheres.

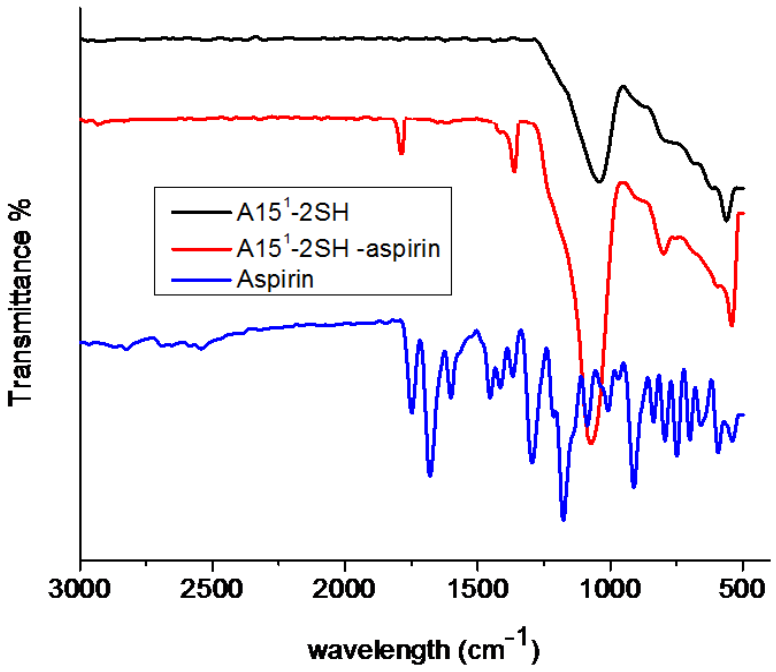


Figure 6.11. shows the FTIR spectra of aspirin and functionalized A15[1]-2SH aerogel microspheres before and after loading aspirin. After loading aspirin, the sample of the A15[1]-2SH -aspirin shows a weak band at 1700 cm-1, which corresponds to the carboxylic

group of aspirin. This indicated that part of the aspirin molecules interact with pore walls through hydrogen bonding. Two bands at 1470 and 1380 cm^{-1} correspond to the C-H bending vibration in the aspirin molecules. The band at 1760 cm-1 corresponding to COO- groups of aspirin is still present on the spectrum, which also suggests that aspirin does not degrade. Therefore, it further proves that aspirin has been loaded in the $A15^{1}$-2SH aerogel microspheres.

6.3 Evaluation of Capsule

Weight Variation Test

The aspirin loaded aerogel microspheres were filled in to capsule of size 1. Twenty capsules were randomly selected and weighed to determine the average weight and were compared with individual capsule weight. The percentage weight variation was calculated. As per Indian Pharmacopoeial Specification, capsules with an average weight between 80 – 250 mg, the percentage deviation should not be more than ± 7. 5 % and capsules with an average weight more than 250 mg should not be more than ± 10 %.

Table 6.7 Weight variation test for capsules

S.No:	Total Weight of Capsule (mg)	Weight of empty Shell (mg)	Weight of microsphere (mg)	Weight of drug loaded microspheres (mg)
1	211	67	91	143
2	207	68	89	139
3	210	68	90	142
4	212	70	90	142
5	210	68	90	142
6	210	66	91	144
7	205	68	88	137
8	209	71	89	138
9	209	68	90	141
10	211	69	90	142
11	212	67	91	145
12	208	69	89	139
13	211	69	90	142
14	211	68	90	143
15	210	72	88	138
16	212	67	91	145
17	211	70	90	141
18	216	72	91	144
19	211	69	90	142
20	210	68	90	142

The average weight of the 20 capsules was found to be 210.3 mg. The overall percentile weight deviation is found within the limit as the pharmacopeial standards of ± 10%.

2. Drug Release - *In-Vitro*

The prepared formulations then placed in the shaker for the release studies over a period of 24 hours. Since the formulation is a pH sensitive controlled drug release, the release experiments were carried out at both acidic and basic pH in phosphate buffers of pH

2 and pH 7.4. The results showed a drastic difference in the release pattern while comparing the nature of the physiological buffer solutions PBS.

Release Studies at Phosphate Buffer Solution (pH 7.4)

The release of the drug loaded aerogel microspheres which were functionalized with a surface modification with $A15^1$-2 SH illustrated best release in controlled manner. The release was estimated at 79.97 %. The release percentile of $A15^1$-2 NH functionalized aerogels was found to be lower than the $A15^1$-2 SH with 69.41 %. The results were followed by the percentile drug release of 61.17 for the formulation $A15^1$. When compared to the multiporous aerogel microspheres MCM-41 showed abrupt release.

Table 6.8 *In Vitro* Release of $A15^1$-2 SH

Time (hr)	% Drug release	Cumulative % Drug release
0.5	36.19	36.19
1	49.10	50.19
2	64.02	64.2
8	77.89	78.01
12	78.51	78.63
24	79.88	79.97

Figure 6.12. Cumulative % drug release of $A15^{1}$-2SH

Table 6.9 *In Vitro* Release of $A15^{1}$-2 NH

Time(hr)	% Drug release	Cumulative % drug release
0.5	31.3	31.3
1	44.45	44.5
2	56.38	56.45
8	67.49	67.54
12	67.88	67.97
24	69.31	69.41

Figure 6.13. Cumulative % drug release of A15[1]-2NH

Table 6.10. *In Vitro* Release of 4A

Time(hr)	% Drug Relaese	Cumulative % drug release
0.5	31.76	31.86
1	41.69	41.78
2	52.88	53.1
8	59.11	59.2
12	59.61	59.77
24	61.06	61.17

Figure 6.14. Cumulative % drug release of 4A

Table 6.11 *In vitro* release of MCM- 41

Time (hr)	% Drug release	Cumulative % Drug release
0.5	52.51	52.51
1	53.42	53.51
2	53.51	53.52
8	53.77	53.88
12	54.18	54.26
24	56.41	56.49

Figure 6.15. Cumulative % drug release of MCM-41

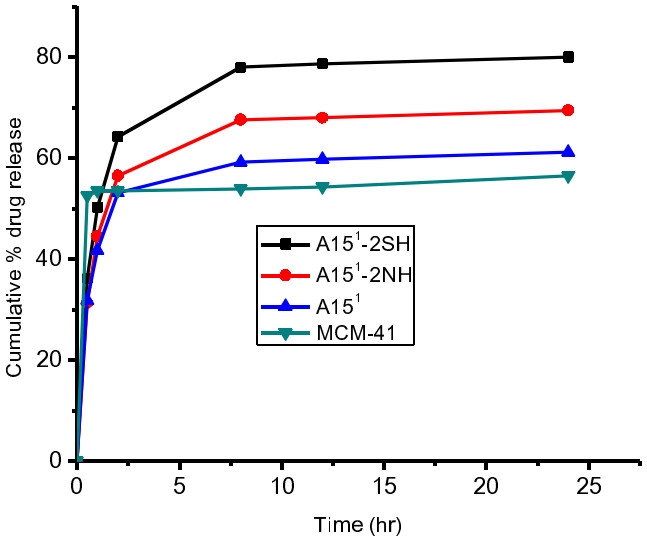


Figure 6.16. Cumulative % drug release collective graph at pH 7.4

RESULTS AT PHOSPHATE BUFFER SOLUTION (pH 2)

The drug release was studied in phosphate buffer of pH 2. The release was examined to show the release rates were well below 20 percent for all the formulations. The amount of drug release trend inverts for the groups carrying $A15^1$-2SH and $A15^1$-2NH.

The inversion in the trend is due to change in the surface charge .This can be explained as these pH sensitive microspheres the drug molecule which does not dissociate from the drug. The percentage of drug release profile was seen to be highest amongst them in $A15^1$-2NH which stands at 15.8%, followed by the $A15^1$-2SH value of 13.8%.

The ordered porous MCM-41 was seen to have a lesser release 11.2% which is least.

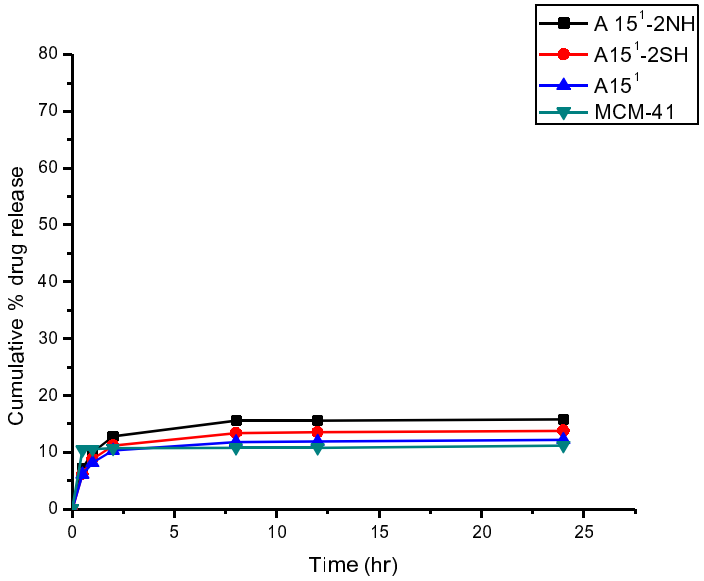


Fig 6.17. Cumulative % drug release at pH 2

Optical images of alumino-siloxane aerogel microsphere

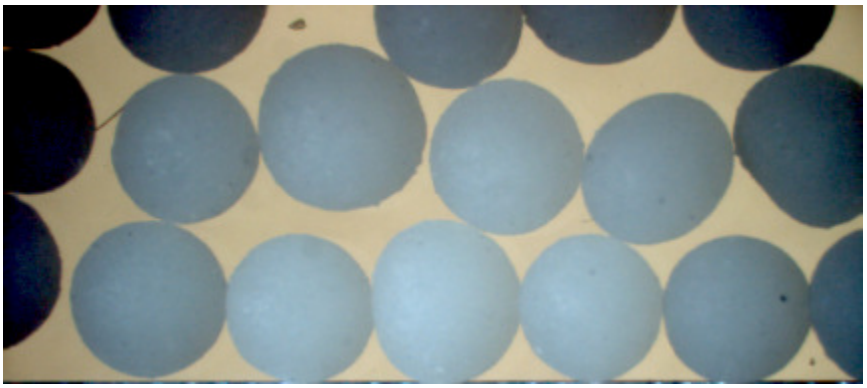
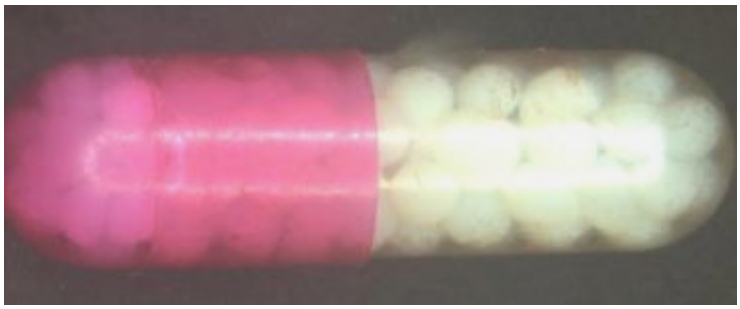
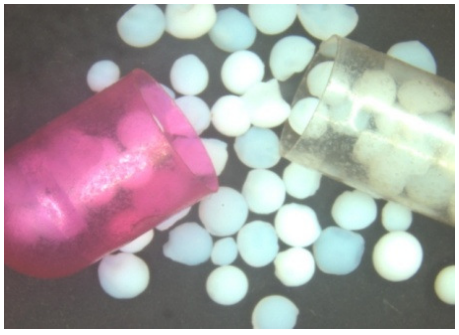


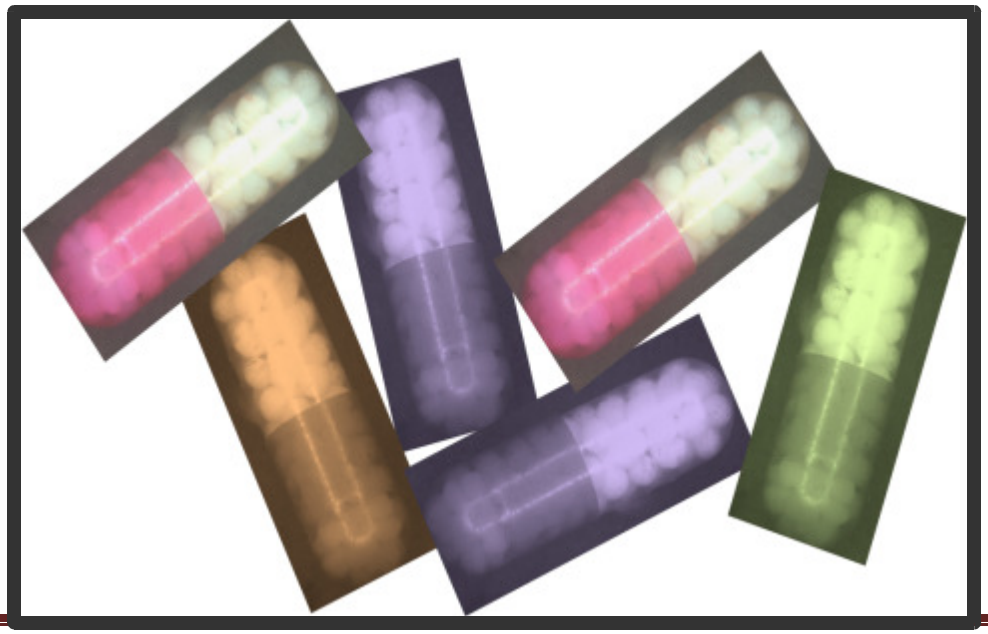
Fig 6.18. Optical microscopy images of aspirin loaded microspheres

Optical images were obtained and the spherical aerogel beads seen with the loaded drug. The images shows the spherical nature of these sphere when observed under high resolution.

Optical images of alumino-siloxane aerogel microsphere filled in capsules







6. CONCLUSION

The work focused on the synthesis of new drug carrier for those drugs which require controlled drug release. The synthesis of this novel carrier brings with it a great hope in future as a potential carrier. The alumino siloxane aerogel microspheres showed both promising drug loading and drug release for which the results were confirmed. The functionalized inorganic multiporous channels act as the suitable candidate for the pH sensitive drug delivery. The drug would be released in the intestinal pH of 7.4 only. The results obtained proved that aerogels acts as a best candidate for the controlled drug delivery; releasing the drug in the required fashion there by increasing the bioavailability of the drug.

Only since the past half a decade the researchers have realized the importance of aerogels in the field on pharmaceutical industry before which its main application was as in insulator in packaging materials. Exploration has been done on silica and funtionalization; but this work was carried out on organically modified alumina silicate which is a step ahead

The technique would be highly cost effective since no binders and enteric coating polymers need to be used. The number of excipients used for the formulation is also very low. This in turn is a novel approach a face changer for most of the drugs.

This work is being extended for studying the biocompatibility of the aerogel microbeads. And it is planned to conduct the experiments on the rat model as a pharmacological evaluation.

Research has to extend to the next level to see this type of dosage form in the market.

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